BRITISH MEDICAL JOURNAL

JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

SATURDAY MAY 6 1961

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BRITISH MEDICAL JOURNAL

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MODERN AIDS TO DIAGNOSIS OF VIRUS DISEASES*

BY

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[WITH SPECIAL PLATE]

We have witnessed in the past 15 years a period of progress unprecedented in the history of medicine, and the very fact that in 1960 virology can be included in a symposium on "Modern Aids to Diagnosis" is sufficient indication of the extent of the progress that has been made. Before the last war diagnostic methods for virus diseases were strictly limited; only a handful of laboratory tests were available, and several of these required elaborate animal tests and were consequently of little practical value in diagnosis. Any diagnostic test for infectious disease, bacterial or viral, depends primarily on a means of culturing the infective agent; all other procedures—for example, the preparation of antigens and serological tests—are dependent on this being achieved first. Viruses were then much more difficult to culture than most bacteria; being intracellular parasites, they cannot be grown on simple lifeless media, such as agar and nutrient broth, but require living cells for their growth. It is very largely due to the advances made in cultural methods that such rapid progress has been made in the study and diagnosis of virus diseases.

Historical Background

Virology is very much a product of the twentieth century, for the first viral agents of infectious disease were recognized at the turn of the century. The foundations had, however, been laid a century before by Edward Jenner; his observations on the natural history of cowpox were to prove one of the great landmarks in preventive medicine.

In March, 1802, evidence was presented to a Select Committee of the House of Commons on the development of the "vaccine inoculation" against smallpox (Jenner, 1805). For some years Jenner had been aware of the protection that accidental cowpox in farm-workers apparently gave against the vastly more virulent smallpox. In his evidence and in other works published during the preceding four years Jenner described in considerable detail the essential differences between cowpox and inoculation smallpox, two diseases we now know to be caused by viruses and antigenically related to each other. He also gave details of the method for carrying out arm-to-arm transfer, emphasizing the need for doing so during the early eruptive phase, and of methods for preserving the "vaccine" in a viable state (Jenner, 1798). All these observations were recorded a good 100 years before viruses were first recognized as agents of disease; they were made by the power of reasoning and observation and without laboratory aids.

Cowpox still occurs in Great Britain, and recent investigations of such cases may serve to illustrate the way in which methods of diagnosis have been developed. While a sick child was being examined on a farm in a village a few miles from Jenner's home in Gloucestershire it was noticed that the father had a solitary ulcerative lesion on the left thumb (Laurance, 1955). On inquiry it was found that several of the cows had vesicles on the udders, which later ulcerated. Serum samples taken from the farmer on days 8 and 22 of the disease showed a specific rise in complement-fixing antibody to both cowpox and vaccinia viruses. In a subsequent case seen a few years later and in an earlier stage of the disease, cowpox virus was isolated both from the cows and from the skin lesions by inoculation of fertile eggs. Apart from its historical interest, this case should underline the value to diagnosis of information about the case. Clinical details, with dates of onset of signs and symptoms, information about previous illnesses and immunizations, and epidemiological data, are of the greatest possible value in deciding what tests can best be used in the individual case and at any given stage of the disease.

The first two human viruses, those of yellow fever and poliomyelitis, were identified in the early 1900's, and since then each decade has seen some other exciting discovery. During the period 1900–29 several other human viruses were isolated—herpes simplex, varicella, measles, mumps, and so on. The presence of specific cellular changes and inclusion bodies in rabies was described in 1903 by Negri, and in yellow fever in 1912 by Rocha-Lima, both of which observations have since formed the basis of diagnostic aids. A few successful attempts were made to grow viruses in tissue culture, and particular mention should be made of the Maitlands, who devised a method of growing tissue fragments in suspended cultures (Maitland and Maitland, 1928). This method was found to support the growth of vaccinia virus, and later was used with various modifications by many other workers. But, generally speaking, the difficulties of virus culture remained paramount.

This period also witnessed a series of major epidemics of infectious disease. Poliomyelitis became epidemic in Western Europe at the turn of the century, with the first severe epidemics in Britain in the summers of 1910 and 1911. In 1918–19 occurred the most lethal and widespread epidemic disease of all times—pandemic influenza—to be followed shortly afterwards by the appearance of epidemic encephalitis lethargica, which

*Paper read in a symposium on "Modern Aids to Diagnosis" at the Annual Meeting of the British Medical Association, Torquay, 1960.

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remained prevalent for a number of years. At the time there were virtually no laboratory tests available for the study of these epidemics, and our knowledge of them comes from historical records.

During the 1930's a new series of techniques for culturing viruses in the embryonated egg were described by Goodpasture (1933) and Burnet (1936). More viruses were isolated, among them influenza, psittacosis–lymphogranuloma inguinale, and the first of the arthropod-borne encephalitis viruses. The adaptation to mice of several strains of virus—influenza, psittacosis, and one strain of poliovirus (Lansing Type 2 strain)—opened up a new way for quantitative measurement of virus and antibody by means of mouse inoculation.

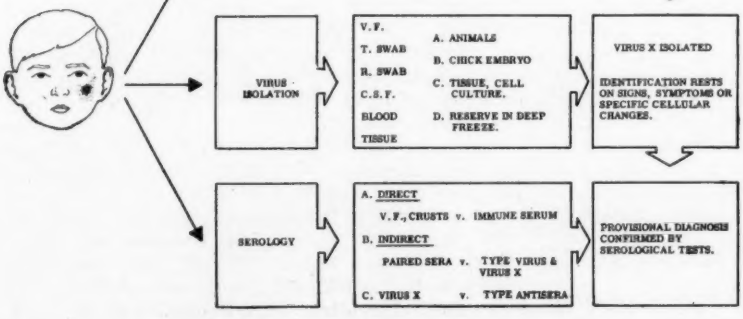
During the 1940's important advances were made in embryonated-egg techniques (Beveridge and Burnet, 1946); the phenomenon of red-cell agglutination produced by the influenza viruses, first recognized in Canada by McClelland and Hare (1941), led to a simple *in-vitro* test for measuring influenza virus and antibody. The antibiotics, which had made a rather unobtrusive entry into medicine during the war years, proved to be a most valuable aid in the virus laboratory. Since they had no effect on viruses, antibiotics could be used to prevent or control bacterial infection from developing in inoculated eggs or cell cultures without recourse to filtration, or some other method, as a means of removing bacteria. And, finally, in 1949 came the most important single contribution of the whole half-century with the discovery, at the Children's Medical Center in Boston, that poliovirus could be grown in tissue culture and in cells of non-neural origin (Enders *et al.*, 1949). This was indeed the break-out. For years virologists had striven to overcome the principal obstacle to the study of poliomyelitis—the predilection of the virus for primates and for nervous tissue. Now all this was altered by a comparatively simple technique, and the way was open for rapid advance.

The reintroduction of tissue culture has had far-reaching results, and the 1950's have already seen the first harvest of these new techniques, a subject that was dealt with in detail by Dr. Rhodes last year (Rhodes, 1960). One outcome of using these new culture methods on such an extensive scale was the isolation of a host of "new viruses." As many of these were found in apparently healthy as well as sick people, the problem resolved itself into defining causal relationship between organism isolated and disease entity (Huebner, 1957). As a result of applying a modified twentieth-century version of Koch's postulates some order has now become apparent in the aetiological classification of several groups of viruses. Ten years ago we recognized influenza A and B of the respiratory viruses, and the C strain had just been isolated. Evidence to support the viral aetiology of the common cold, "acute respiratory disease," and atypical pneumonia came from experiments on human volunteers. Now we recognize as the cause of respiratory disease adenoviruses, parainfluenza viruses, influenza viruses, the virus of atypical pneumonia (Eaton agent), certain enteroviruses, and a large miscellaneous group awaiting classification, including viruses associated with the common cold. Similarly, in 1950 we recognized poliovirus and the Coxsackie virus as aetiological agents in non-paralytic poliomyelitis and aseptic meningitis; now we think in terms of a group of viruses—the enteroviruses consisting of polioviruses, Coxsackie A and B, and the E.C.H.O. group, responsible for a wide spectrum of disease ranging from paralysis and aseptic meningitis to mild febrile illnesses. Much more is now known about the encephalitis viruses, and the important group of "arbor" viruses has now been classified on a serological basis into four sub-groups—A, B, C, and a miscellaneous group (Casals and Reeves, 1959). None of this would have been possible without great improvements in diagnostic procedures (Francis, 1956).

Principles and Methods of Diagnosis

Laboratory tests, to be of any value in diagnosis, must be quick and reliable. The whole tempo of virological procedures has altered, and there are now several ways in which a provisional diagnosis can be made quickly in the early stages of the disease. Final confirmation may still take some time, as it invariably depends on the result of a serological test. There are three lines of approach to diagnosis (see Diagram): (1) *microscopy*: examination of infected tissues for the presence of virus or the effect of virus; (2) *virus isolation*: isolation of the infective agent from the tissues or secretions known to be involved in the disease process; and (3) *serology*: demonstration of an immune reaction, specific in nature and related in time to the disease process under investigation. (V.F. = vesicle fluid; T. and R. = throat and rectal swab.)

DIAGNOSIS OF VIRUS DISEASES



The decision to use any test or set of tests must depend on the individual case. For example, cytological or histological examination is applicable only when the lesion or eruption is on the surface of the body or with biopsy or post-mortem material. Cytological examination of smears or wet films has the advantage that results can be obtained quickly. Virus culture is becoming increasingly important as a means of diagnosis, and is the method of preference during the acute

phase of the illness. It is now possible to make a provisional diagnosis in a few days by isolation of the causal agent, and the significance of this will be even greater if the isolation has been made direct from the blood, cerebrospinal fluid, or tissues rather than from the throat or faeces. Serological diagnosis, except in specific instances, depends on comparing an acute with a convalescent sample of serum, and the result must therefore be retrospective. Another difficulty in serological diagnosis is the multiplicity of serological types of many virus groups and, consequently, the large number of antigens that may have to be used. For example, there are at present at least 18 strains of adenovirus, 28 of E.C.H.O. virus, and 24 of Coxsackie virus. To test for all of them would be impracticable, and it is therefore usually preferable to concentrate first on virus culture. If a virus is isolated it has to be identified by its cultural and serological characteristics in much the same way as bacteria or other micro-organisms are identified in the laboratory.

Serological procedures based on antigen–antibody reactions can be used in a number of ways: (1) to demonstrate viral antigen by means of a specific reference antiserum; (2) to measure the antibody response to infection by testing an acute and convalescent sample of serum against reference strains of virus; and (3) to establish the antigenic relationship of any agent isolated from the patient. These tests are simpler and more straightforward with viruses with a single serological type—for example, measles, variola, herpes simplex; with those having a limited number, such as the three strains of poliovirus; or with some of the respiratory viruses possessing a common or group antigen.

Collection of Material

The procedures to be observed for collecting material for virus diagnosis have been published in detail (Francis, 1956), so only a few practical points need to be stressed here. (1) Material for virus isolation should be collected fresh as early as possible in the disease and maintained at a suitably low temperature. It is important to ensure that material for virus isolation, such as throat or rectal swabs, is not allowed to dry. For this purpose it should be placed in some suitable fluid medium containing a small amount of serum devoid of viral antibodies. (2) Blood samples should be separated as soon as possible to prevent haemolysis, and the serum (not whole blood unless asked for) sent to the laboratory. (3) Adequate information on the patient—name, age, clinical details with dates of onset of illness—with details of specimens and investigation required should accompany the specimens. Instructions about transport to the virus laboratory must be carefully observed.

Examination of Material

1. Microscopy

Microscopical examination of material from cutaneous lesions is of value in the vesicular and early pustular stage of smallpox, vaccinia, varicella–zoster, and herpes simplex. Smears should be taken from the base of the lesions on clean glass slides and allowed to dry. Different stains can be selected to show the general cytological picture (Giemsa), elementary bodies (Paschen or Gutstein), and inclusion bodies (haematoxylin and eosin) (Special Plate, Fig. 1). Cytological details can also be clearly seen in films prepared by the wet-film method introduced by Dudgeon and Patrick (1927) for the diagnosis of malignant growths by exfoliative cytology. Smears are fixed "wet" in Schaudinn's fluid and stained by Mayer's haemalum and a weak solution of eosin (Dudgeon and Wrigley, 1935). This method is useful for the study of vesicular and bullous eruptions, but is not satisfactory for the study of elementary bodies.

(*a*) *Elementary Bodies* (*E.B.s*) *or Virus Particles.*—The elementary bodies of variola–vaccinia were first described by Buist, of Edinburgh, in 1886 in tissues infected with vaccinia virus. Some years later Paschen recognized the importance of examining for E.B.s in diagnosis of smallpox, and the stain he described—"Paschen's stain"—is still widely used to-day. In smallpox E.B.s are present in great numbers during the early stages of the eruption and, after staining by Paschen's or Gutstein's method, can be seen by ordinary light microscopy (Downie, 1959) (Special Plate, Fig. 1). In vaccinia the E.B.s are less numerous, and in varicella and herpes simplex they are just too small to be seen by ordinary light microscopy, so that the test has definite limitations.

(*b*) *Cytological Changes.*—In herpes simplex and varicella–zoster the changes in epithelial cells seen in smears made from the base of vesicles are characteristic. Multinucleate epithelial giant cells and margination of the nuclear chromatin are constant findings, but intranuclear inclusions can also be found, particularly in preparations stained with haematoxylin and eosin. These changes are similar in both infections and are to be found at an early stage in the disease; they are not found in variola or vaccinia, and hence their diagnostic value (Special Plate, Fig. 1).

In a series of 38 cases of generalized herpes simplex in children the diagnosis was confirmed by this method in 30 (Brain, 1956). As herpes virus can cause a severe disease in infants and young children, especially those with eczema, early recognition of the aetiology can help to prevent spread to other susceptible children (Dudgeon, 1958).

Multinucleate cells have also been described in nasopharyngeal secretions in measles (Beale and Campbell, 1959). These giant cells are different in appearance from those seen in herpes and varicella–zoster, but as they can be demonstrated in the pre-eruptive stage an early diagnosis can be made before the appearance of the rash. (Special Plate, Fig. 1.)

Intracytoplasmic inclusion bodies can also be found in epithelial scrapings from cases of inclusion conjunctivitis. In the differential diagnosis between this condition and gonococcal ophthalmia it is advisable to examine epithelial scrapings and not just a film of the exudate.

Exfoliative cytology can also be used in the diagnosis of cytomegalic inclusion disease. Epithelial cells with intranuclear inclusions have been reported in urinary sediment in a number of cases (Robbins, 1959).

2. Biopsy and Post-mortem Material

There are many occasions when microscopical examination is of value in virology; some examples are shown in Special Plate, Figs. 1 and 2. It is of particular importance in the diagnosis of rabies. Rabies has not been a hazard in the United Kingdom since quarantine regulations were introduced some years ago, but in many other countries it is still a major public-health problem. In the Province of Ontario there has in recent

years been a sharp increase in the number of reported cases of rabies, both in wild and in domestic animals—2,000 cases were reported in 1958 (Fenje and Amies, 1960). One confirmed case has been reported in a child (McLean *et al.*, 1960). The finding of intracytoplasmic inclusions in the brains of animals suspected of rabies was first described by Negri in 1903. Smears should be made from Ammon's horn and from the cerebral and cerebellar cortex by the impression method to preserve the anatomical configuration, and stained by Sellers's or van Gieson's method (Johnson, 1959). Brain material should also be retained for virus isolation by animal inoculation. Negri bodies stand out as well-defined inclusion bodies within the cytoplasm of nerve-cells (Special Plate, Fig. 1). As Negri bodies can be found in a high proportion of dogs infected with rabies, microscopical examination provides an important diagnostic procedure and a guide to the treatment to be adopted.

In cases of sudden death in children histological examination has often led to the diagnosis. During the poliomyelitis outbreak in Great Britain in 1953 three cases of sudden death in young children were at necropsy found to have signs of acute encephalitis. In one case, that of a 17-day-old infant who died suddenly in hospital after an operation, the diagnosis of poliomyelitis was suspected. At necropsy the diagnosis of poliomyelitis was confirmed by histological examination of the central nervous system and by isolation of the virus in a monkey (Pugh and Dudgeon, 1954). The other two cases, in older children, were diagnosed in the same way. Subsequently all three strains were shown by tissue-culture tests to be Type 1 strains. In general, histology should be regarded as an important ancillary aid to the diagnosis and investigation of virus disease requiring special study.

Virus Culture

The use of laboratory animals and embryonated eggs for virus culture and the many improvements in technique during the past 15 years have been well documented (Rhodes and van Rooyen, 1958). Despite the advances in tissue and cell culture, the use of the embryonated egg remains a convenient and sensitive method for isolating a number of viruses, among them those of influenza and mumps, the pock viruses—variola, vaccinia, and cowpox—and also herpes simplex virus. These last-mentioned grow readily on the chorio-allantois, producing within two or three days focal necrotic lesions which are fairly distinctive on naked-eye examination, especially those of vaccinia and cowpox, and are of great value in early diagnosis; but final identification must take into account the results of other tests. This is particularly important in the diagnosis of smallpox. Some examples of the lesions produced by viruses on the chorio-allantois are shown in Special Plate, Fig. 3.

In 1948 Dalldorf and Sickles (1948) isolated a virus in baby mice from the faeces of two children with paralytic poliomyelitis. This observation led to the recognition of the Coxsackie viruses, the first group of enteric viruses antigenically distinct from poliovirus. The Coxsackie viruses have been classified into two main groups. The group A strains, consisting of about 24 different types, produce marked weakness in baby mice as a result of a generalized myositis. Group B strains, consisting of five different types, produce tremors and spastic paralysis with focal necrosis of muscle and viscera. Group B strains grow well in tissue culture (Dalldorf *et al.*, 1959), but only a few group A strains will do so. Coxsackie A viruses have been recovered from cases of herpangina and aseptic meningitis by inoculation of pharyngeal washings, faeces, and cerebrospinal fluid into baby mice. Group B strains play an important role in human disease, having been consistently recovered from cases of Bornholm disease, aseptic meningitis, infantile myocarditis, and acute pericarditis. Recently Steigman (1958) has reported that certain non-polioviruses, Coxsackie A and B and E.C.H.O. viruses, can cause encephalitis and paralytic disease. The use of baby mice is therefore an important feature of the modern virus laboratory.

Tissue or Cell Culture

By far the most practical method of virus culture is tissue or cell culture. Several such methods are available, each with its own attributes, but all based on the same principle that tissues removed from the animal host can be cultured in a suitable nutrient medium in glass containers (Enders, 1959). There are many advantages to be gained with these techniques. Virtually any animal species within reason can be selected—simian, human, rabbit, chick, and so on—and the same freedom of choice applies to the organ selected for culture—for example, kidney, amnion, lung, testis, muscle. Further, cells grown in culture are not affected by the animal's immune mechanism. The use of antibiotics in the growth medium enables cultures to be kept free from bacterial contamination, while at the same time the growth of virus is not affected.

For diagnostic purposes one method in particular, trypsinized monolayer cells, has been found particularly useful. The idea of using trypsin to disperse tissue fragments for culture purposes was first conceived by Rous and Jones in 1916, but the method was not apparently used again for more than 30 years until Scherer *et al.* (1953) reintroduced it for the large-scale preparation of cells maintained in continuous culture. Several other workers about the same time, among them Dulbecco and Vogt (1954) and Youngner (1954), described the value of trypsin for the preparation of monolayer cultures. Trypsin breaks down tissue fragments into aggregates or single cells, depending on the time the trypsin is allowed to act. If the cell aggregates are freed from trypsin by light centrifugation and washing in a buffered salt solution, resuspended in a nutrient medium, and dispersed into stationary glass vessels the cells will settle out, adhere to the glass, and then begin to grow out as a monolayer. After a few days' incubation discrete islands of cells will be found on microscopical examination, and after a few further days' incubation the cells appear as a continuous sheet under the microscope. Cultures can be grown in many types of glass vessel—flasks, "medical flats," or tubes—and, provided the medium is changed at regular intervals, the cells can be maintained for several weeks in a satisfactory state. For detailed study of cytopathology tube cultures are particularly useful, as they can be examined directly under the microscope. Permanent preparations of the cells can be made by embedding the cell sheet in celloidin and staining or by growing the cells on coverslips placed in the tubes. Some examples of monolayer cells prepared and stained in this way are shown in Special Plate, Fig. 4. This method can be used for primary cultures of monkey kidney, amnion, and rabbit kidney, and many others as well. Second-generation

cultures can be made in the same way. Many laboratories also hold in stock cultures of established cell lines which have been maintained by serial passage of cells derived from some human or animal source. The HeLa cell, isolated from a cervical carcinoma (Gey *et al.*, 1952), is widely used for diagnostic purposes, as are other human carcinoma cells, such as the HEp2 and Eagle's KB strain (1955). Other cell lines in use are the epithelial cells from normal conjunctiva, liver, kidney, and appendix isolated by Chang (1954), and a human amnion cell by Fogh and Lund (1957).

Another extremely useful method is the monolayer with agar overlay. Dulbecco and Vogt (1954) described a method of preparing trypsin-dispersed cells in Petri dishes, preferably grown in the incubator in an atmosphere of 3% CO_2 in air. Cells grow over the glass surface of the Petri dish as a monolayer. The cells should then be washed with a buffered saline solution, the virus inoculum added, and after a short interval a few millilitres of melted agar and nutrient medium containing neutral red is added as an overlay to the cells. After a few days' incubation the effect of virus growth is evident by the presence of plaques due to the local destruction of cells. Hsiung and Melnick (1955) have devised a useful technique based on this method in which the monolayer cells with overlay are grown in tightly stoppered bottles, thus obviating the need for a special humidified incubation and supply of CO_2.

The virologist uses tissue culture in the same way as the bacteriologist does a medium of agar or broth. In many instances material for virus isolation—for example, throat and rectal swabs, vesicle fluid, or material taken at necropsy—will be contaminated with bacteria ; unless these are controlled the cultures themselves will become contaminated. Light centrifugation and the addition of 500 units of penicillin and 500 μg. of streptomycin per ml. is usually sufficient to control the growth of bacteria in the inoculum. For every set of cultures inoculated it is essential to set aside uninoculated cultures as controls. The cultures can be placed in a roller-drum or kept stationary in an incubator. They should be examined at regular intervals for evidence of virus growth, inoculated cultures always being compared with controls.

Viruses, being intracellular parasites, are recognized by the effect produced on the cells in which they multiply. In this respect they vary considerably, from viruses that produce cell damage visible under the microscope to those that produce no obvious cellular change and in which the presence of viral antigen can be recognized only by a serological reaction. The main methods for recognizing virus growth in cultures are set out below.

(*a*) *Cytopathic Effect (C.P.E.).*—A large number of viruses produce cell necrosis which can be detected under the microscope (Special Plate, Figs. 5 and 6). The C.P.E. varies from one virus to another in character, time of appearance, and extent of involvement. For example, viruses that normally produce inclusion bodies as part of their pathological process also tend to do so in tissue culture. Measles, herpes simplex, vaccinia varicella–zoster, and Simian B virus are a few of those that can be recognized in this way. Others—for example, the enteroviruses and adenoviruses—produce cellular changes of a less specific nature, but, with experience, the discerning eye can often be reasonably certain of the agents involved.

(*b*) *Haemagglutination and Haemadsorption.*—Several viruses—for example, those of the respiratory group—grow in various forms of cell culture, but produce little or no cytopathic change, thus making it difficult to determine whether or not virus growth has occurred. Influenza viruses can be isolated in monkey kidney cells, but the cytopathic changes, which seldom involve the whole sheet of cells, are not so specific as those already described. But a haemagglutinin is produced, as occurs with influenza viruses growing in the fertile egg. If fowl or guinea-pig red cells are added to the cultures haemagglutination occurs if influenza virus is present, and in the same way the antigenic type (A or B) can be determined by the haemagglutinin-inhibition test. Other members of the myxovirus group—for example, the para-influenza viruses—produce no C.P.E. or haemagglutinin on primary isolation, but can be detected by the haemadsorption test recently described by Vogel and Shelokov (1957). Red cells, on being added to virus-infected cultures, are adsorbed on to the cells, an effect readily detectable under the microscope (Special Plate, Fig. 7). This technique provides a convenient method for identification of the myxoviruses (influenza, para-influenza, mumps, Newcastle disease) and vaccinia virus.

Until recently the evidence for the multiplication of "common cold viruses" in cell cultures prepared from human embryonic tissue could be established only by inoculation of human volunteers, as no cytopathic changes could be detected. Later it was found that cultures infected with these viruses, although appearing normal, were resistant to infection with another virus, such as Sendai virus (para-influenza)—an example of the interference phenomenon. More recently Andrewes and his colleagues (1959) have shown that a C.P.E. can be demonstrated with these viruses if the cultures are grown in a medium with a reduced bicarbonate and increased glucose concentration and by incubation at 33° C.

(*c*) *Fluorescent Antigen–Antibody Test.*—Yet another method of identifying viruses that produce no obvious cytopathic change, haemagglutination, or haemadsorption is by fluorescent microscopy. Coons (1941, 1958) developed a technique for demonstrating antigen–antibody reactions by ultraviolet microscopy. If antibody is labelled with a fluorescent dye and then applied like a histochemical stain to infected tissues containing viral antigen the reaction between antigen and antibody can be demonstrated under the ultra-violet microscope by the presence of a green fluorescence in infected cells.

Serological Tests

Recovery from a virus infection is accompanied by the production of circulating antibody and a period of resistance to the infecting strain of virus. Serological tests for antigen and antibody form an integral part of virological procedures, and, despite the limitations already referred to, constitute one of the most important diagnostic tools in current use. The scope of serological diagnosis has been greatly enhanced by the recognition of many new viruses, and therefore of diagnostic antigens. Methods of preparation and purification of these antigens have been improved. By the use of tissue-culture methods it is now possible to carry out neutralization and other serological tests on a scale that would have been quite impracticable by any other method, and at the same time with a greater degree

of accuracy. Several well-established techniques, such as complement-fixation, flocculation, and agglutination, have been improved and adapted to virological work, while other entirely new techniques—gel-diffusion and fluorescent microscopy—have been introduced.

The limitations of serology in diagnosis must be recognized. First there is the time factor. Time must be allowed for the immune response to develop, and, if neutralization tests are to be used, a further period for completion of the test; thus the results must be retrospective. Secondly, there is the problem of the multiplicity of immunological types, with several groups of virus to be borne in mind. This is of particular importance with the enteroviruses and the respiratory viruses. In such cases antibody tests against the whole range of antigens is impracticable as a routine measure, so that some form of screening of specimens becomes necessary unless an alternative method is available. Thirdly, it should be remembered that the interpretation of results on the basis of antibody titres alone, particularly with single specimens, is difficult unless adequate information about the case is available. The date of onset of symptoms and the date of collection of the serum are essential in this respect.

1. Neutralization Tests

Neutralizing antibody is the most important indication of past infection and is the antibody closely concerned with protection. It is produced as a result of both clinical and subclinical infection and as a response to active immunization. It is highly specific, and is therefore used for identification of virus strains into immunological types. Altogether the presence or absence of neutralizing antibody is of considerable significance in diagnosis and in epidemiological surveys. In a neutralization test a serum is examined for its capacity to prevent, modify, or "neutralize" the effect of a virus by inoculation of serum–virus mixtures into a cell system in which the virus by itself is known to produce an effect. For example, herpes simplex virus produces focal lesions on the chorio-allantois, and certain strains of influenza virus will produce pneumonic consolidation if inoculated into mice by the intranasal route. If, however, serum–virus mixtures are inoculated, lesions or symptoms are prevented, provided the serum contains antibody specific to the virus. Such tests require large numbers of fertile eggs and experimental animals if quantitative estimations are to be made. Fortunately, many such tests, but not all, can now be carried out in tissue-culture with a considerable saving in time and expense. Monolayer cultures of monkey kidney cells and HeLa cells are used extensively for neutralization tests, but other cells can be used provided they are susceptible to the virus under test.

There is no single method suitable for all neutralization tests, but in general principle the procedure is as follows:

Serum–virus mixtures are prepared by adding equal volumes of diluted virus suspension (the titre having been previously determined) to aliquots of inactivated serum in serial dilution. Serum–virus mixtures are allowed to stand at room temperature or in the refrigerator for an appropriate length of time in order to allow neutralization to take place. Small quantities of the serum–virus mixtures are then inoculated into suitable cell cultures. Appropriate controls of virus by itself and known positive and negative sera should always be included. Inoculated cultures are then incubated, and examined at regular intervals, usually on the third and seventh days. The presence of antibody is determined by comparing the tubes containing serum–virus mixtures with the controls. The antibody titre is taken as the highest dilution of serum in which a proportion of the cultures are infected and a proportion protected (50% end-point). The determination of the end-point depends on the culture system and virus under test. Several alternative methods are available.

(*a*) *The Cytopathic Method.*—This can be used for estimating antibody against those viruses which produce degeneration of cells. Antibody to the enteroviruses and many others can be titrated in this way by direct microscopical examination. For example, polio-antibody will protect monkey kidney cells from destruction by poliovirus, and, as the reaction is specific, sera have to be titrated separately against the three strains of poliovirus. In the same way antibody to herpes, measles, and adenovirus can be titrated using the cytopathic changes as an index of unneutralized virus of the serum–virus mixtures.

(*b*) *The Metabolic-inhibition or Colour Test.*—This test is a useful alternative to the cytopathic test. Serum–virus mixtures prepared in the same manner are tested in a series of small tubes or in plastic panels consisting of several rows of cups or depressions. To these are added a known quantity of trypsinized cells in suspension. The medium used in the test contains an indicator, phenol-red, which changes colour from red to yellow according to the metabolic rate of the cells. In the cups or tubes containing uninoculated cells metabolism continues, with the colour changing to yellow owing to a lowering of *p*H from the accumulating metabolic by-products. Cells infected with virus are destroyed, so the *p*H rises, as reflected by a change to deep red or even purple. With serum–virus mixtures a fall in *p*H (red to yellow) indicates neutralized virus due to protection by antibody; a rise in *p*H (red to yellow) indicates unneutralized virus. The end-point is reached when the colour is changed in approximately 50% of the cups or tubes containing the highest dilution of serum.

These methods have been used extensively in recent years for the estimation of polio-antibodies in both diagnostic and epidemiological work. The results obtained by the cytopathic method and colour test compare favourably with each other and show a high degree of consistency. The colour test is easier to read, as it does not involve such prolonged examination of cultures under the microscope.

(*c*) *Haemadsorption-inhibition.*—Antibody to the myxoviruses can be measured in tissue-culture by means of the haemadsorption phenomenon. Guinea-pig red cells (0.4%) are added to monolayer cultures of monkey kidney inoculated with serum–virus mixtures. Haemadsorption can be seen under the microscope in cultures containing unneutralized virus, whereas those containing neutralized virus show no such effect (Chanock *et al.*, 1958). Haemadsorption can be demonstrated with all the myxoviruses in a variety of cell cultures, and with the red cells of several species—human, fowl, and guinea-pig.

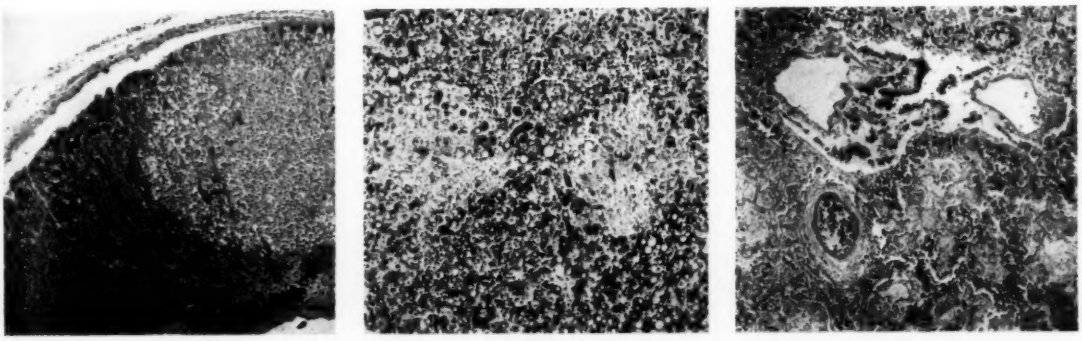
2. Complement-fixation (C.F.) and Haemagglutinin-inhibition (H.I.) Tests

Improvements in technique have led to the production of purified and concentrated antigens, and with the growing recognition of the importance of controls the accuracy of these tests has been considerably enhanced (Lennette, 1956, 1959). Antibody in the myxoviruses can also be measured by the haemagglutinin-inhibition test. Both C.F. and H.I. tests can conveniently be carried out on trays or in plates made of "perspex."

The complement-fixation test is of particular value in the study of respiratory virus infections, as antibody to several of these viruses—influenza, adenovirus, parainfluenza, and respiratory syncytial viruses—can be detected by this means. With other newly recognized

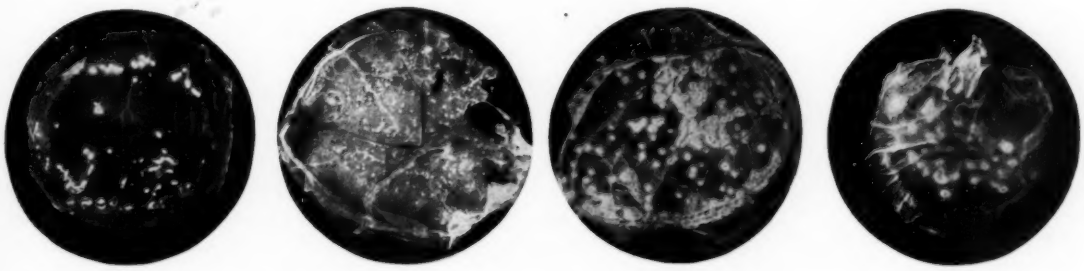
(a) (b) (c) (d)

FIG. 1.—(*a*) Elementary bodies of variola. (Gutstein's stain; ×800.) (*b*) Multinucleate cells in herpes simplex. (Giemsa; ×200.) (*c*) Multinucleate cells in measles. (×166.) (*d*) Negri bodies in impression smear. (Sellers's stain; ×233.)



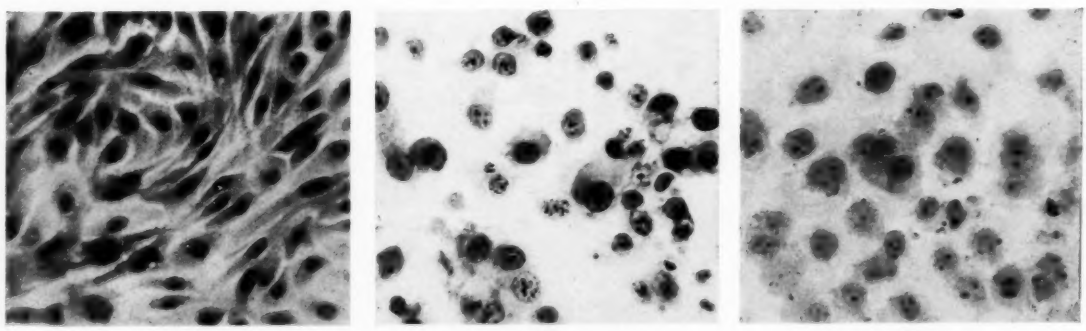
(a) (b) (c)

FIG. 2.—(*a*) Adrenal necrosis in herpes simplex. (×80.) (*b*) Hepatic necrosis in prolonged generalized vaccinia. (×80.) (*c*) Pulmonary necrosis in disseminated varicella. (×105.)



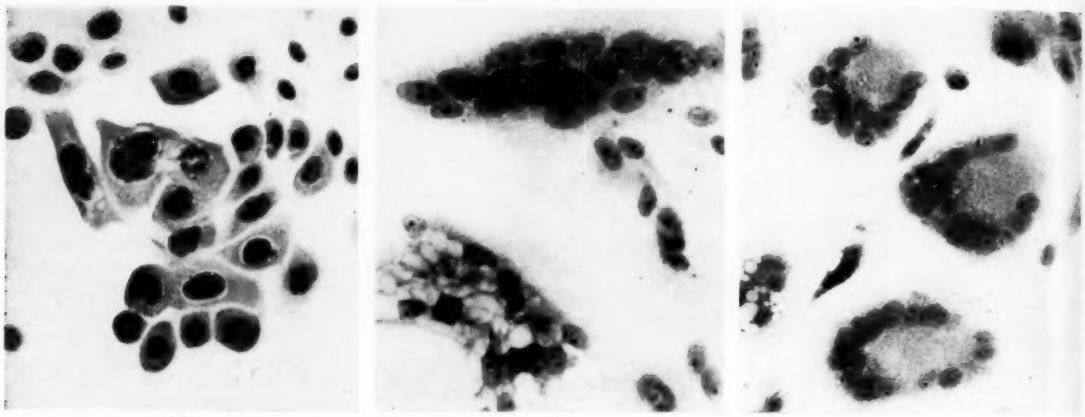
(a) (b) (c) (d)

FIG. 3.—Focal lesions on chorio-allantois produced by viruses. (*a*) Variola. (*b*) Herpes simplex. (*c*) Vaccinia. (*d*) Cowpox.



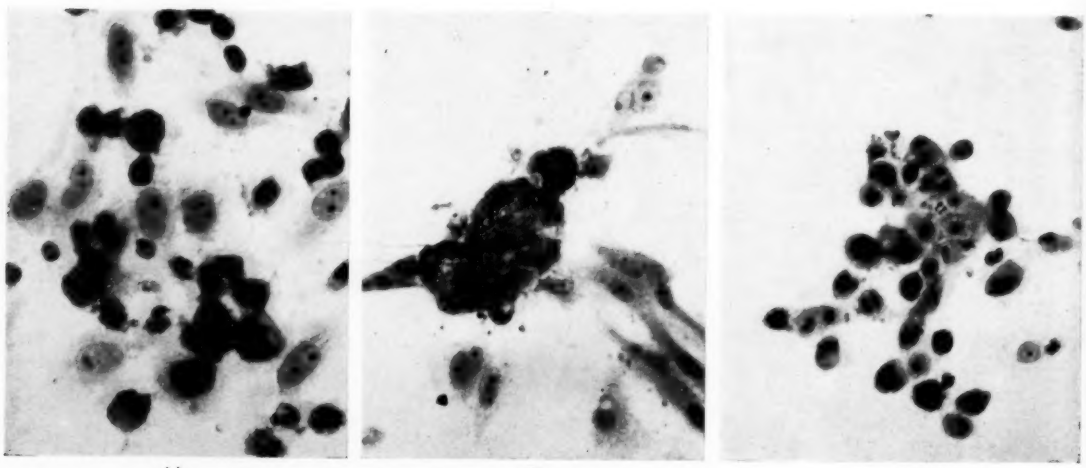
(a) (b) (c)

FIG. 4.—Monolayer cultures of normal cells. (*a*) Monkey kidney. (*b*) Human amnion (continuous). (*c*) Epithelial carcinoma cell (H.Ep. 2). (All stained by haematoxylin and eosin. ×250.)



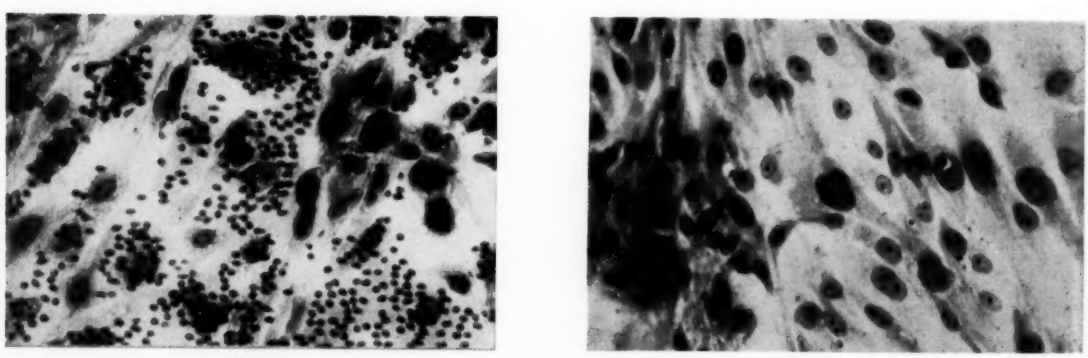
(*a*) (*b*) (*c*)

FIG. 5.—Cytopathic effect of viruses on monolayer cultures. (*a*) Herpes simplex in human amnion. (×280.) (*b*) "Wild" viruses in monkey kidney. (×200.) (*c*) Measles virus in human amnion. (×200.) (All stained by haematoxylin and eosin.)



(*a*) (*b*) (*c*)

FIG. 6.—Cytopathic effect of viruses in monkey kidney monolayer cultures. (*a*) E.C.H.O. type 9. (*b*) Croup-associated (para-influenza 2). (*c*) Adenovirus. (All stained by haematoxylin and eosin. ×280.)



(*a*) (*b*)

FIG. 7.—Haemadsorption phenomenon. Monkey kidney monolayer cultures infected with para-influenza 3 virus. (*a*) Guinea-pig red cells adsorbed to cells injected with virus. (*b*) Control culture; no haemadsorption.

viruses the C.F. test either is less sensitive or cannot be used owing to the lack of a satisfactory complement-fixing antigen.

3. Fluorescent Antibody Technique

The technique of fluorescent microscopy described by Coons (1958) can be used to measure the antibody responses to an agent producing little or no obvious effect in inoculated culture—as, for example, the Eaton agent isolated from cases of primary atypical pneumonia. A method for measuring antibody in this agent by the indirect method has been described by Liu and his associates (1959).

Lungs of chick embryos infected with the Eaton agent by amniotic inoculation are removed and sectioned on the freezing microtome. The sections are then fixed on glass slides in acetone. To suitable sections containing bronchiolar epithelium are added dilutions of the serum under test. After incubation for a short period the slides are washed with buffer, and an anti-human-globulin conjugated with fluorescein is then added. After further incubation the slides are examined by ultra-violet microscopy. The labelled globulin localizes at points where antigen–antibody reaction has occurred, producing a yellow-green fluorescence.

By this method the antibody titre in acute and convalescent samples of sera can be estimated (Liu *et al.*, 1959).

4. Tests for Viral Antigen

Serological tests can also be used to detect viral antigen in the tissues in the acute phase. In smallpox there is such a heavy concentration of viral antigen in the skin that material taken from vesicles, pustules, or crusts can be used in a direct serological test with a positive serum (vaccinial) as control. The C.F. test is the best known of these, but recently Dumbell and Nizamuddin (1959) have described an agar-gel precipitation based on the Ouchterlony technique. Antigen (variolous material) and antibody (vaccinial serum) are allowed to diffuse towards each other on an agar surface. Reaction between antigen and antibody is indicated by an opaque line at the line of precipitation. The test is specific and very quick, taking only a few hours to read.

Complement-fixation can also be used for the identification of newly isolated strains of influenza virus. Lief and her associates (1958) have described a C.F. test which permits rapid identification of strains by means of strain-specific antisera.

Most Recent Advances

The striking advances of the last few years are a sure indication of the value of these new laboratory methods and their practicability. Ten years ago, when tissue culture was just being revived, the diagnosis of poliomyelitis was confined to a few laboratories with facilities for inoculation of monkeys. The measurement of polio-antibody was virtually prohibitive, because only one strain (Type 2) could be measured in a small laboratory animal, the mouse; antibody to Types 1 and 3 could be assayed only in monkeys. This required a large number of monkeys for titration of a single serum. Nowadays with tissue culture the kidneys from one monkey provide enough cultures to make possible titration of several pairs of sera against all three types of virus and with a high degree of accuracy. Another great advance has been the isolation and identification of new respiratory and enteric viruses. Originally these were termed "orphan" viruses, as their relation to human disease was not apparent; but considerable progress has been made in relating these new viruses and immunological types to various disease entities (Andrewes, 1959; Macrae, 1959).

The value and accuracy of virus isolation methods are shown by the number of isolations made from cases of paralytic and non-paralytic poliomyelitis. In the accompanying Table are shown the number of isolations made at four different centres during the period 1955–9. The figures for Canada for 1959 were kindly supplied by Dr. D. M. McLean, The Hospital for Sick Children, Toronto, and are particularly illuminating, as they show a 100% isolation rate of poliovirus from paralytic poliomyelitis and underline the importance of the other enteric viruses in non-paralytic poliomyelitis and aseptic meningitis. The viruses isolated from this latter group consisted of several different types—Coxsackie A 9; Coxsackie B 2, 3, 4, and 5; E.C.H.O. viruses 6, 9, and 14; and a few which could not be typed (McLean, 1960). Recent attention has been drawn to the role of some of these viruses as a cause of severe disease, particularly in infants. The virulence of herpes simplex in the newborn has been recognized in recent years; Coxsackie virus has been named as a cause of infantile myocarditis; and Steigman (1958) and others have shown that severe paralysis and encephalitis can be caused by Coxsackie and E.C.H.O. viruses. Much has still to be learnt of the importance of these viruses, but with the diagnostic tests available this should now be possible.

It is interesting to speculate on what the findings would have been if the methods here described had been available during the great epidemics that occurred in Great Britain in the early part of the century. Would we have found, for instance, that Type 1 poliovirus was responsible for the 1911 epidemic, and swine influenza virus for the 1918–19 pandemic, and was herpes simplex really the cause of epidemic encephalitis lethargica? We may never know the real answer to these fascinating questions, but we are certainly now in a strong position to deal with problems of this sort should they occur again. Indeed, we have already done so. The cause of

Table Showing Recovery of Poliovirus in Tissue Culture from Cases of Poliomyelitis in Great Britain and Canada

Place and Year	Paralytic Poliomyelitis					Non-paralytic Poliomyelitis				
	No. of Specimens Tested	Polio-virus	Other Enteric Viruses	No Virus	Recovery of Polio-virus %	No. of Specimens Tested	Polio-virus	Other Enteric Viruses	No Virus	Recovery of Polio-virus %
London, 1955*	43	29	0	14	67	19	7	0	12	37
Home Counties, 1955†	33	31	0	2	95	91	32	11	48	42
Northern Ireland, 1955–7‡	502	434		68	86	734	270	82	382	36
Canada, 1959§	23	23	0	0	100	95	0	33	62	0

* Peach, A. M., and Dudgeon, J. A. (1955). Unpublished data. † Huston, A. F., Morwood, J. B., Christofinis, G. J., and Wood, W. (1956). *Brit. med. J.*, **2**, 629. ‡ Murray, H. G. S., Dane, D. S., and Dick, G. W. A. (1958). *Ulster med. J.*, **28**, 1. § McLean, D. M. (1960). Personal communication.

the Asian influenza epidemic of 1957 was identified and typed within a few weeks after it began in the Far East; but with other virus diseases, such as rubella and hepatitis, we have to report no progress whasoever. These and other diseases still to be tackled constitute a current challenge.

I should like to express my thanks to Dr. D. M. McLean, The Hospital for Sick Children, Toronto, for the impression smear from a case of rabies (Special Plate, Fig. 1) and for the data regarding virus isolations in Canada (see Table); to Dr. D. A. J. Williamson, the Children's Hospital, Southampton, for the material from the case of disseminated varicella (Special Plate, Fig. 1); also to Dr. A. J. Beale for the smear from a case of measles (Special Plate, Fig. 1) and for much helpful advice. I am also grateful to Mr. D. Boxall, Photographic Unit, Glaxo Laboratories Ltd., and to Mr. Derek Martin, Department of Medical Illustration, The Hospital for Sick Children, Great Ormond Street, London, for help and advice in preparing the illustrations.

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FAT-MALABSORPTION IN CONGESTIVE CARDIAC FAILURE

BY

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It is a well-recognized fact that many patients suffering from congestive cardiac failure of long duration tend to lose weight, and this has generally been ascribed to anorexia. The possibility that malnutrition has resulted from malabsorption seems to have been largely unexplored, and in this paper an attempt is made to assess the frequency of steatorrhoea in cardiac failure.

Material and Methods

The 20 cases studied were all in-patients of St. Thomas's Hospital, and in each case the diagnosis of the cause of cardiac failure was made by the physician in charge of the case. In 17 of the cases this cardiac failure, as judged by jugular venous pressure, was present during the investigation—in three cases the venous pressure had fallen to normal from three to seven days before the tests were begun.

Patients received a normal ward diet, although in some cases anorexia resulted in a diminished intake of food. An attempt was made to grade the anorexia in each of these cases. After an oral dose of 10–20 μc. of I-131-labelled triolein given in 10 g. of arachis oil, the faecal output of radioactivity was measured and expressed as a percentage of the dose received by the patient. Stool saves were made for from three to six days, and in most cases the faecal total lipids were measured as well and expressed as grammes per day (Prunty *et al.*, 1959). Results below 3% were regarded as normal for faecal I-131 triolein and those between 3 and 7% necessitated parallel faecal-fat estimation for their proper evaluation. Above 7% the results were regarded as abnormal (Vaughan Jones, 1960). Faecal total lipids above 7 g. a day were regarded as abnormal for persons eating a normal ward diet (Annegers *et al.*, 1948; Wollaeger *et al.*, 1947). Conventional liver-function tests were performed in most of the patients.

Results

The results obtained are shown in the Table. All the cases except Nos. 3 and 18 were receiving treatment with digitalis. It will be noted that Cases 1–5 all had evidence of fat-malabsorption as judged by one or other of the two tests. Only in Cases 1 and 3 was malabsorption demonstrated by both tests. Case 2 had high faecal fat and normal faecal radioactivity; Cases 4 and 5 had high faecal radioactivity and normal faecal fat.

Discussion

In this group of 17 patients in congestive cardiac failure, three had steatorrhoea as judged by chemical fat estimation. One of these cases had normal radioactive fat excretion, but it is generally considered that the correlation between these tests is less than perfect and in particular that the triolein test tends to miss steatorrhoea (Pimparkar *et al.*, 1960; Vaughan Jones, 1960).

In Cases 4 and 5 a high output of faecal radioactivity coexisted with a normal faecal fat. There are two possible explanations. First, the anorexia and consequently diminished food, and therefore fat, intake of these patients may have masked steatorrhoea. Such masking is well documented for low fat intakes (Wollaeger *et al.*, 1947; Frazer, 1949; Weijers and van de Kamer, 1953; Crowe *et al.*, 1956). Secondly, the discrepancy may represent a further failure of the I-131 triolein test. Van Handel and Zilversmitt (1958) have shown that I-131 triolein is absorbed differently from triolein labelled with C-14 and presumably therefore from triolein itself, possibly because of breakdown of the former during absorption. However, in congestive cardiac failure because of anorexia it is often not possible to guarantee a sufficient intake of fat to validate estimation of daily faecal fat as a test of malabsorption, and therefore one may underestimate the occurrence of malabsorption. Perhaps therefore one should not too lightly discard this isotopic evidence of malabsorption in Cases 4 and 5, especially since where discrepancies occur between faecal fat and iodinated triolein estimation they are usually, as already indicated, on the side of normal iodinated triolein and high faecal fat. Thus it is certain that three and possible that five of 17 patients with congestive cardiac failure showed evidence of fat-malabsorption, clearly a much higher incidence than in the general population.

Examination of the Table indicates that three of these five patients had shown moderate or considerable loss of weight, and, although appetite was classed as moderate in each of the three, the possibility exists that fat-malabsorption as well as anorexia had played some part in the genesis of this loss of weight. However, three other patients with cardiac failure in the present series, in whom steatorrhoea was not demonstrated, lost weight to an equivalent amount.

It remains to be explained why these patients with cardiac failure had steatorrhoea. Digitalis, so commonly prescribed to such patients, was suggested as a cause (A. C. Dornhorst, personal communication, 1958), but one of the patients with steatorrhoea was not receiving digitalis and 14 patients receiving digitalis did not have steatorrhoea. If a cause at all, digitalis is clearly not the only cause nor a very potent one. No obvious correlation emerged between the chronicity of cardiac failure and steatorrhoea, nor between any particular cause of cardiac failure and steatorrhoea.

There appeared to be little correlation, either, with evidence of liver damage as judged by conventional liver-function tests except that the serum bilirubin level was slightly raised in three patients out of the four with steatorrhoea in whom it was measured. It was raised in only one of the 11 patients without steatorrhoea in whom it was measured.

Only one account of the presence of steatorrhoea in patients with cardiac failure has been found: de Langen (1953) states that steatorrhoea is occasionally present—

Table of Results

Case No.	Diagnosis*	Faecal Fat (G./day)	Amount of Administered Radioactivity in Faeces	Weight Loss	Appetite	Duration Present Cardiac Failure	No. of Previous Admissions for Cardiac Failure	Serum Bilirubin (mg./100 ml.)	Thymol Turbidity (units)	Plasma Alkaline Phosphatase (K–A units per 100 ml.)	Serum Protein (g./100 ml.)		
											Total	Albumin	Globulin
Group I: In cardiac failure at time of test													
1	MS	10·1	55·4	Slight: ½–1 st. (3.2–6·4 kg.) in 1 year	Moderate	4 weeks at least	Nil	2·4	3	14	6·8	2·9	3·9
2	MS MI TI	8·4	1·6	Striking: 2½ st. (15·9 kg.) in 5 years	,,	Chronic failure	Numerous	1·3	1	27	6·0	3·3	2·7
3	H	8·5	4·3	Nil	Good	4 weeks	Nil	1·2	7	9	6·8	3·8	3·0
4	MS MI TI	2·9	12·6	,,	Moderate	4 ,,	7	—	—	—	—	—	—
5	MS MI TI	6·5	9·5	Striking: 2 st. (12·7 kg.) in 2 years	,,	2 months	3	0·6	2	—	—	—	—
6	MS MI TI	3·9	6·3	Nil	Poor	Chronic failure	Several	0·5	3	20	—	—	—
7	AI	6·3	1·0	,,	Good	4 weeks	2	0·5	1	19	7·0	4·2	2·8
8	H CP	1·8	2·0	,,	Poor	Chronic failure	2	—	—	—	—	—	—
9	MS MI TI	5·2	—	Striking: 4 st. (25·4 kg.) in 7 years	Good	4 weeks	10	0·5	3	17	6·1	4·2	1·9
10	MS MI AI	—	1·0	Nil	Moderate	4 ,,	1	0·6	1	8	5·8	3·4	2·4
11	MS MI	—	1·0	,,	Good	2 ,,	3	0·5	2	8	6·7	3·3	3·4
12	CP	2·4	0·5	,,	,,	3 ,,	2	—	—	—	—	—	—
13	Unknown	2·8	3·7	,,	,,	10 days	4	0·5	7	12	7·6	3·7	3·9
14	H	5·2	2·1	Striking, but had deliberately dieted	,,	2 weeks	1	0·4	2	8	5·7	3·5	2·2
15	MS MI	5·9	1·0	Nil	,,	2 months	1	0·7	3	8	6·2	3·4	2·8
16	MS	2·5	1·3	,,	,,	5 weeks	2	0·9	2	34	8·0	4·5	3·5
17	MS MI	—	1·4	Striking: 2 st. (12·7 kg.) in 2 years	Poor	4 months	2	1·8	1	38	5·7	3·4	2·3
Group II: No longer in cardiac failure at time of test													
18	MS MI	5·4	1·0	Slight	Good	Cured 1 week before test	Nil	—	—	—	—	—	—
19	MI	4·8	0·5	Nil	,,	Cured 3 days before test	,,	0·8	4	17	7·4	3·4	4·0
20	IHD	3·2	0·9	,,	,,	,, ,,	,,	—	—	—	—	—	—

* MS = mitral stenosis; MI = mitral incompetence; TI = tricuspid incompetence; AI = aortic incompetence; H = hypertension; CP = cor pulmonale; IHD = ischaemic heart disease.

"even in cases of cardiac decompensation with hypertension in the portal area considerable quantities of fat may occasionally be found in the stools."

A recent paper includes a comparison between the plasma levels of radioactivity obtained after an oral dose of I-131 triolein in patients while in congestive cardiac failure with those obtained after recovery (Berkowitz *et al.*, 1959). Few details were given, but low levels of plasma activity were said to revert to normal after recovery from cardiac failure.

It is known that disturbed liver function is often found in patients with chronic cardiac failure. This is especially so in those with constrictive pericarditis and rheumatic valvular disease, in particular mitral stenosis with tricuspid incompetence (Koletsky and Barnebee, 1944; Sherlock, 1951; White *et al.*, 1955). Analogy with infective hepatitis and cirrhosis suggests that the findings of Gross *et al.* (1950) in these diseases may be relevant. Fat-malabsorption, which they assumed to be due to lack of bile salts, correlated moderately well with the serum bilirubin concentration and roughly inversely with faecal sterobilinogen output.

Other possible explanations for fat-malabsorption in cardiac failure are pancreatic and intestinal malfunction. Masoni and Pellegrini (1953) have demonstrated impaired pancreatic function in patients with severe chronic cardiac failure, and Meakins (1940) thought that such patients had an intestinal absorption defect for glucose; de Langen (1953) suggested that intestinal congestion or ischaemia in cardiac failure might explain fat-malabsorption. It is possible that one of these two explanations may apply in the cases described, but the point was not investigated further.

Summary

Fat-malabsorption has been demonstrated in 3 out of 17 patients with congestive cardiac failure and may have been present in two more. No correlation with cause or chronicity of cardiac failure, loss of weight, or digitalis therapy was observed. The possible significance of the raised serum bilirubin in three of the cases of fat-malabsorption is discussed.

I am grateful to Dr. R. R. McSwiney, Dr. J. L. Pinniger, and Professor F. T. G. Prunty for help, and to the physicians of St. Thomas's Hospital who have allowed me to study their cases.

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ULCERATIVE COLITIS AND PARATHYROID DYSFUNCTION

BY

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A significant proportion of patients with hyperparathyroidism have concomitant peptic ulceration (Rogers, 1946), and a recent survey of a group of 300 consecutive peptic-ulcer patients (Frame and Haubrich, 1960) resulted in the discovery of hyperparathyroidism in 4. The hyperparathyroidism precedes and in some as yet undefined way provokes the ulceration. The association of pancreatitis and hyperparathyroidism is also recognized, but this relationship is more obscure. It has been suggested that the hypercalcaemia causes intraductal calcium precipitation with blockage, but such deposition is not always present, and in one patient the pancreatitis appeared to precede the hyperparathyroidism (*British Medical Journal*, 1959).

Steatorrhoea has been observed in combination with hypoparathyroidism (Jackson, 1957; Williams and Wood, 1959) and more rarely hyperparathyroidism (Davies *et al.*, 1956). Again the link is perceived but the mechanism of association remains to be elucidated.

These examples of the coexistence of gastro-intestinal and parathyroid disorders lend interest to the presence of hypoparathyroidism and hyperparathyroidism, respectively, in two patients with long-standing ulcerative colitis, who were treated with steroids.

Case 1

A 40-year-old white physician was seen in January, 1957, because of cramps in the extremities. His relevant history went back approximately 20 years, when he first experienced attacks of mild diarrhoea which recurred every few months. In 1947 the diarrhoea became more severe and was accompanied by a blood-stained rectal discharge. In 1951 he again had severe diarrhoea and in addition frank rectal bleeding. He was admitted to a London hospital, and after investigation, which included a barium enema and a sigmoidoscopy, the diagnosis of ulcerative colitis was made. He returned to South Africa and a year later developed severe pain and some swelling of the joints of the fingers, wrists, ankles, and knees, for which hydrocortisone was prescribed in a dosage of approximately 60 mg./day. Both the diarrhoea and the arthritis lessened, and this treatment was continued for two years, until 1955, when severe diarrhoea recurred, with marked loss of weight. It was thought that the steroid dosage was inadequate, and prednisone 40 mg./day was substituted. The diarrhoea subsided and the prednisone was slowly reduced to 20 mg./day. He gained weight and felt stronger, but experienced carpal spasms which were ascribed to hyperventilation. He later attended a hospital in San Francisco, where the diarrhoea became worse and was accompanied by severe carpal spasms, paraesthesias of the extremities, and tingling around the mouth.

Laboratory tests at the time revealed: serum calcium, 5.5 mg./100 ml.; serum phosphorus 5.7 mg./100 ml.; serum protein, 6.1 g./100 ml. (albumin 3.6 g., globulin 2.5 g.), and alkaline phosphatase 4.4 King–Armstrong units.

He was told that his symptoms resulted from the steroid therapy, but attempts to reduce the dose provoked such severe diarrhoea that intravenous-fluid therapy was necessary. He was given parenteral calcium and calciferol, 200,000 units/day. Thyroid function was reported as normal. He then visited another clinic, where reduction of

the dose of prednisone again caused incapacitating diarrhoea. Because of continued deterioration an ileostomy and a subtotal colectomy were eventually done at a London hospital. He was extremely ill during the post-operative period, losing large amounts of fluid from the ileostomy. Eight months after the first operation the rectum was removed and the prednisone discontinued. Some weeks later he again had severe generalized spasms almost amounting to opisthotonos, but after intravenous calcium therapy these subsided. Approximately two weeks later he felt tremulous, his neck was enlarged, and his pulse rate became rapid with runs of ectopic beats. There were no spasms at this time. A diagnosis of thyrotoxicosis was made, being confirmed by a radioactive iodine uptake test. Methylthiouracil was prescribed, the symptoms abated, and he gained weight. He returned to South Africa, but shortly after arrival the cramps returned, affecting the feet, calves, and hands.

Physical examination in January, 1957, showed him to be tall and thin—height 6 ft. (183 cm.), weight 120 lb. (54.4 kg.)—and mentally alert. Slight exophthalmos was present and the thyroid gland was moderately enlarged and smooth. The heart and lungs were normal, and the blood-pressure was 120/76 mm./Hg. The ileostomy appeared healthy. Both the Chvostek and the Trousseau signs were positive. The reflexes were brisk and the plantar responses flexor. There were numerous fine excoriations of the skin and he complained of generalized pruritus. Slight swelling with restriction of movement of the proximal joints of the fingers was present.

Laboratory Investigations.—The relevant biochemical tests, which were repeated several times over a period of a few days, gave the following results: calcium, 4–6.4 mg./100 ml.; phosphorus, 5.6–6.8 mg./100 ml.; alkaline phosphatase 8.2–8.8 K–A units; total protein, 6.9–8 g./100 ml. (albumin 2.2–4.1 g., globulin 3.8–4.7 g.); urea, 24 mg./100 ml.; Sulkowitch reaction in urine, 0–14. The serum electrolytes were normal, the haemoglobin 13.4 g./100 ml., and the leucocyte count 5,600, with a normal differential count. The urea clearance was 102%. An electrocardiogram showed Q–T prolongation compatible with hypocalcaemia. Skeletal *x*-ray films revealed generalized decalcification. A four-day fat balance showed over 95% absorption.

A diagnosis of hypoparathyroidism with hypocalcaemic dermatitis (Dent and Garretts, 1960) was made and therapy with dihydrotachysterol instituted. He was given initially 3 ml. daily, and this was decreased gradually to a maintenance dose of between 0.4 and 0.8 ml. daily. The cramps were alleviated and the serum concentration of calcium rose and that of phosphorus fell. However, when taking sufficient dihydrotachysterol to cause complete disappearance of tetany the Sulkowitch reaction in the urine would become strongly positive. As he had had urinary calculi in the past, fear of calcium precipitation in the urinary tract prompted him to reduce his dose of dihydrotachysterol. He found that with a smaller dose of dihydrotachysterol tetany could be averted by a concomitant reduction in the dose of methylthiouracil. Since then he has controlled his own treatment, remaining relatively well by balancing mild hypocalcaemia with mild thyrotoxicosis. His main disability at present is periodic pains in the joints which, fortunately, respond to salicylates. He has gained approximately 15 lb. (6.9 kg.) in weight, carries out his normal professional activities, and feels stronger than he has done for years.

Case 2

A 29-year-old white male clerk was seen in April, 1960, because of generalized weakness and a painful swelling of the right calf.

Diarrhoea first occurred soon after an automobile accident some 10 years earlier. He felt very depressed at that time, ate little, and lost approximately 40 lb. (18.1 kg.) in weight. He had three or four loose dark stools daily. After six months of illness he first consulted his doctor. A presumptive diagnosis of amoebiasis was made and various drugs were prescribed, without benefit. The diarrhoea persisted, and in 1954, after approximately four years of illness, he was admitted to the Johannesburg General Hospital, where, on radiological examination of the colon and sigmoidoscopy, a diagnosis of ulcerative colitis was made.

A year later the diarrhoea became worse and he developed severe pain and swelling of the joints of the fingers, wrists, elbows, feet, and knees. He was readmitted to hospital and steroid therapy begun. Initially cortisone was prescribed, but this was later changed to methylprednisolone and again to dexamethasone. Maintenance therapy with dexamethasone was continued up to the present episode. Both the arthritis and the diarrhoea improved on steroids and he was able to resume work. The stools continued to be loose, but he was not incapacitated.

His general state of health was fairly satisfactory until January, 1960, when he first experienced renal colic and passed gravel in the urine. More or less simultaneously he developed polydipsia and polyuria and severe nocturia. His appetite diminished and he again lost weight.

In April he was readmitted to hospital because of generalized weakness and a tender swelling of the right calf. After admission the diarrhoea became severe and a few days later nausea and vomiting occurred and he complained of an unpleasant metallic taste. He had not taken excessive quantities of milk or alkalis nor any vitamin D.

Physical examination revealed an extremely ill, apathetic, dehydrated man. Blood-pressure 100/50 mm. Hg. His mouth and tongue were so dry that speech was difficult. Apart from the dehydration, he appeared to have lost much weight. The presence of band keratopathy was questioned but could not be confirmed. Apart from a tender, warm, swollen right leg, the remainder of the examination was negative.

Laboratory investigations, made in May, resulted as follows: Calcium, 13.4–17.7 mg./100 ml.; phosphorus, 4.6–5 mg./100 ml.; alkaline phosphatase, 7.3–12.6 K–A units; total protein, 6.3 g./100 ml. (albumin 3.5 g., globulin 2.8 g.); urea, 57–130 mg./100 ml.; 24-hour urinary calcium, 375 mg. The serum electrolytes were normal, the haemoglobin 9.2 g./100 ml., and the leucocyte count 11,400, with an eosinophilia of 10%. Skeletal *x*-ray films revealed no abnormalities and dental films showed a normal lamina dura.

It was considered that the high concentration of calcium in the serum while he was on steroid therapy did not favour the diagnosis of sarcoidosis or inadvertent vitamin D overdosage, and a diagnosis of hyperparathyroidism and thrombosis of the calf veins was made. Intravenous fluid therapy was vigorously pursued and heparin administered. Despite a slight fall in the concentration of calcium in the serum, severe anorexia and nausea persisted to a degree that precluded oral maintenance, and he remained gravely ill. The left leg also became tender and swollen and he became disorientated, particularly at night. As his condition was deteriorating it was felt that the only possibility of improvement lay in the removal of the offending parathyroid. An emergency operation (Dr. M. Lautre) was done under local anaesthesia and a parathyroid adenoma (weight 3.4 g.—chief cell histology) was readily located and removed.

The patient suffered no ill effects from the operation itself, and the post-operative course was uneventful. The metallic taste, nausea, and anorexia disappeared and he was soon able to take fluids by mouth. The leg thrombosis subsided with no residual oedema. The serum calcium level returned to normal, as did the urea.

Discussion

Both patients had long-standing ulcerative colitis and had received steroids for some years. The first patient developed hypoparathyroidism, which was unrecognized for some time and which was then masked by the onset of thyrotoxicosis with its hypercalcaemic effect (Rothenberg and Redleaf, 1959). When the thyrotoxicosis was controlled the hypoparathyroidism again became

manifest. The problem of the appearance of hypercalciuria at relatively low serum-calcium levels while on treatment with dihydrotachysterol (Litvak *et al.*, 1958) has complicated his management. The second patient, critically ill with parathyroid poisoning, was cured by operation.

Possibly this association between parathyroid disorder and steroid-treated ulcerative colitis is purely fortuitous. Against this possibility is a previous report of the appearance of tetany in a patient with ulcerative colitis receiving steroid therapy (Moehlig and Steinbach, 1954). While the hypoparathyroidism might be explained by parathyroid involvement in a multisystem disease known to affect the skin, joints, eyes, liver, and kidneys as well as the bowel, the cause of the adenoma formation would remain obscure. Furthermore, one might expect that the steroid therapy which lessens the other manifestations of the disease might prevent parathyroid involvement, but in fact the opposite appeared to be the case.

A possible explanation for the association is that in severe long-standing ulcerative colitis calcium stores are reduced either through poor absorption or excessive excretion via the bowel. The use of steroids with their "anti-vitamin D" effect (Anderson *et al.*, 1954) might cause further embarrassment to the already depleted calcium stores. The effect of this might be a need for increased quantities of "para-thor-mone" resulting in either exhaustion, hypoparathyroidism, or adenoma formation.

Summary

Two patients with long-standing ulcerative colitis treated with steroids developed hypoparathyroidism and hyperparathyroidism respectively.

Both have fairly active arthritis, even though the first case has had a complete colectomy.

The tetany and cramps in the first case became more pronounced after colectomy and have persisted for four years. These symptoms respond to dihydrotachysterol, but he has a low renal threshold for calcium and a persistently positive Sulkowitch reaction in his urine. Furthermore, he has hyperthyroidism controlled by methylthiouracil.

The second case, one of hyperparathyroidism, presented with generalized weakness and a phlebothrombosis of his calf veins. He had had an episode of urolithiasis three months prior to admission. His condition deteriorated so rapidly after admission that he had to be subjected to an emergency operation for removal of a parathyroid adenoma, of chief-cell histology, with cure of his hyperparathyroidism.

The possible mechanism for this association of parathyroid dysfunction and ulcerative colitis is discussed.

We are grateful to Dr. B. M. Bloomberg and Dr. W. M. Politzer, who performed the biochemical investigations.

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PHENYLBUTAZONE SUPPOSITORIES IN TREATMENT OF NON-SPECIFIC PROCTITIS

BY

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Recently the topical treatment of ulcerative colitis has come again into prominence. Truelove (1956, 1958). Schwartz *et al.* (1959), and others achieved a rapid clinical remission by local—that is, rectal—hydrocortisone. According to Truelove (1960) a better result is to be expected in moderate and mild cases from local treatment than from systemic prednisolone therapy. Local treatment has several advantages over systemic: (1) the active material acts directly on the diseased mucosa; (2) a greater local concentration can be attained; and (3) complicating side-effects are avoided.

We have successfully used local phenylbutazone treatment in ulcerative colitis (Hankiss and Keszthelyi, 1960; Hankiss, 1961). We tried this drug because of its excellent anti-inflammatory effect, and practical experience has supported our theoretical supposition. A rapid remission occurred in the responsive cases. This was similar to the results achieved by local hydrocortisone. The only essential difference was that, in contrast to Truelove's observations, the extent of involvement proved to be of decisive significance in the case of local phenylbutazone treatment. When the disease was limited to the distal part of the colon our results were good, whereas with diffuse colitis or with colitis involving mainly the right side of the colon local phenylbutazone was ineffective.

This treatment was given in the form of enemata which were excellently tolerated by the patients. It sometimes happened that the patients improved both subjectively and objectively but sigmoidoscopy still revealed a moderate hyperaemia above the anal ring. We thought that the enematas might maintain the inflammation here in a mechanical way and therefore we gave the phenylbutazone as suppositories. With this treatment the signs of inflammation soon disappeared.

At this time we began to be systematically engaged with the suppository treatment of non-specific proctitis.

Selection of Cases

The nature of non-specific proctitis is a debatable question. Some investigators (Thaysen, 1934; Brooke, 1953, 1954) consider it an independent unit, while others (Newell and Jones, 1958; Truelove, 1959) regard it as a concurrent phenomenon of ulcerative colitis. I hold to this second school of opinion, although in some cases of *primary proctitis* the process does not extend to the upper parts of the colon even after a long history. They show fewer general signs and are more benign *quoad sanationem*. We must bear in mind also the *secondary proctitis* which accompanies some other processes, as, for example, anal fissure, fistula-in-ano, haemorrhoids, perianal eczema, pruritus ani, helminthiasis, and post-radiation proctitis. These are usually mild forms of proctitis, without bleeding. Nevertheless they must be treated, because either they can exacerbate the underlying process—for example, perianal eczema or pruritus—or they may produce very unpleasant symptoms.

Our patients were selected after a very careful clinical examination. The cardinal complaints were the passage of mucus and blood per rectum and tenesmus. Mucus and blood were usually found on the surface of a formed stool. Diarrhoea was rare and the general health of the patients has usually remained good.

Besides digital examination, sigmoidoscopy, and examination of the stool, we carried out a barium-enema examination, made a helminthological examination, and excluded amoebiasis.

The classification of our patients into two groups of proctitis—proctosigmoiditis and ulcerative colitis—was made according to the extent of the alterations, the case history, and clinical findings. Here we deal only with those cases of ulcerative colitis in which the process was limited to the most distal part of the colon.

The effect of treatment was assessed by the bowel movements, the disappearance of bleeding and mucus, and especially by the sigmoidoscopic findings.

Method.—Three types of suppositories were used: (1) containing 200 mg. of phenylbutazone; (2) containing 200 mg. of phenylbutazone and 8 mg. of prednisolone; and (3) containing 200 mg. of phenylbutazone, 8 mg. of prednisolone, and 100 mg. of "protargol," incorporated in normal base.

Results

22 patients were treated with suppositories: brief individual details are given in the Table. At the beginning of the treatment we always used suppositories containing only phenylbutazone (Formula No. 1). At first the suppositories were used twice a day—one in the evening and the other in the morning, after defaecation. In a week or two the dose was reduced to one a day, and in two to three weeks, if the patient was then symptom-free, to one in two days, and later on to two a week.

If there was no improvement with phenylbutazone suppositories within 7 to 10 days, then, after discontinuing treatment for some days, we passed to the other types of suppositories. At first we used formula No. 2, but recently have preferred to employ the third one, the protargol of which adds to the anti-inflammatory activity and confers antibacterial properties, too.

Seven out of 11 patients with proctitis showed rapid and lasting remission. One improved on combined suppositories only. In Case 4 a relatively good state could be maintained after relapse only by the administration of combined suppositories. Four of our patients did not require any treatment. In the case of the other improved patients the symptoms returned when we discontinued the 1–2 suppositories weekly, but the patients again became symptom-free when the suppositories were resumed.

The patients with ulcerative colitis did not respond satisfactorily. Only two out of seven are still symptom-free and even those were not really cases of ulcerative colitis. The refractory cases did not respond to combined suppositories either.

The secondary cases responded satisfactorily. Naturally, here the primary causes must be treated first—for example, helminthiasis was cured with the appropriate procedures; and pruritus ani due to eczema perianale got proper treatment. We began suppository treatment only if, after improvement of the primary cause, sigmoidoscopy still showed evidence of proctitis. In all but one case the treatment was followed by a subjective relief of symptoms, and the signs of inflammation disappeared. Here formulae 2 and 3 proved to be best. Prednisolone alone seems to be not so effective as when in combination with phenylbutazone. That is to say, the two drugs seem to potentiate each other's effectiveness.

In regard to effectiveness, two factors appear to be decisive: (1) the duration of the disease (Truelove, 1959)—old, chronic processes respond badly; and (2) the underlying cause. Naturally one can expect a relapse with a progressive ulcerative colitis much more than with pure proctitis. The secondary processes responded in a satisfactory manner only if the primary disease could be healed.

Discussion

In the treatment of chronic proctitis phenylbutazone has proved to be very efficient when used in the form of suppositories. Without doubt, in most part, proctitis cannot be considered an independent unit but is a form of ulcerative colitis (Goligher, 1953; Truelove, 1959). We know, however, that in the case of ulcerative colitis the lesion of the distal part of the colon is often the most serious one, and sometimes only this part is affected, the proximal colon being relatively intact. In

Clinical Details and Response to Phenylbutazone Suppository Treatment

Case	Sex and Age	Length of History	Diagnosis*	Response* to Treatment	Subsequent Course	Length of Observation
1	M 46	8 months	Proctitis	Remission	Symptom-free	2 years
2	M 35	1 month	,,	,,	,,	3 months
3	M 54	4 years	,,	Slight	No improvement on combined suppositories	6 ,,
4	M 36	7 months	,,	Remission	Relapse. Improvement on combined suppositories	10 ,,
5	F 40	6 ,,	,,	,,	Symptom-free	5 ,,
6	M 46	1 month	,,	,,	,,	7 ,,
7	M 29	3 months	,,	,,	,,	8 ,,
8	F 34	1 year	,,	,,	,,	4 ,,
9	M 47	6 years	,,	No	No improvement on combined suppositories	7 ,,
10	M 46	16 months	,,	Slight	Improved on combined suppositories	4 ,,
11	F 38	4 years	,,	No	—	—
12	F 29	3 months	Ulc. colitis	Good	Relapsed	2 years
13	F 36	2 years	,,	Slight	Requires constant treatment	14 months
14	F 34	2 ,,	Proctosigmoiditis	Remission	Symptom-free	5 ,,
15	M 48	10 months	,,	,,	,,	7 ,,
16	F 60	10 years	Ulc. colitis	No	No improvement on combined suppositories	3 years
17	M 42	1 year	,,	Slight	Relapse. Improved on combined suppositories	2 ,,
18	F 39	4 years	Proctosigmoiditis	No	—	—
19	F 18	2 ,,	Proctitis sec. Pruritus ani	Good	Symptom-free	16 months
20	F 36	2 ,,	,, ,,	Slight	Requires constant treatment	10 ,,
21	M 51	4 months	Proctitis sec. perianal eczema	,,	Improved on combined suppositories	1 year
22	F 36	2 years	Sec. proctitis. Helminthiasis	Good	Symptom-free	4 months

* Clinical and sigmoidoscopic.

such cases Truelove (1959) achieved a good clinical remission in 14 out of 22 cases with hydrocortisone suppositories.

Phenylbutazone is known to possess several actions, such as anti-inflammatory (Wilhelmi, 1949; Belart, 1949), reduction of capillary permeability (Wilhelmi, 1949, 1950), and antihistaminic (Domenjoz, 1952). Its local effect is also proved (Heilmeyer *et al.*, 1953) and we have previously used it with success for the local treatment of ulcerative colitis. The drug gets into the deeper layers of the mucosa, too, as was demonstrated by Hawkins and Fawns (1959), who investigated its absorption from the rectum. In our above-mentioned observations we pointed out that the direct contact of the drug with the diseased area is the decisive factor influencing its effectiveness. Our present observations also support this view.

The severity of the inflammatory process does not seem to determine the success of treatment. The decisive factor is the localization of the process. We could achieve success even with a lesion reaching the sigmoid colon if the enemata described above were given for some days before suppository treatment.

Phenylbutazone, by reducing inflammation and capillary permeability, as well as by its antihistamine effect, is beneficial to the inflamed mucosa. Phenylbutazone and prednisolone used in combination seem to potentiate each other's effect (Wilhelmi and Domenjoz, 1951; Kuipers, 1959; Châtel, 1960). They may have a different mechanism of action; this is supported by the fact that in some cases only the one drug, in other cases only the other, is effective.

We have never encountered the ulcerogenic side-effects of phenylbutazone either in suppository form or in enemata. On the contrary, its use in cases of ulcerative colitis and proctitis has resulted in rapid improvement of ulcers and in stopping bleeding.

It should be noted that all treatments of this kind must be preceded by thorough-going proctological examinations to establish the diagnosis and to exclude lesions such as carcinoma.

Summary

Phenylbutazone is well known to be an anti-inflammatory agent, and this property applies to its local use.

Suppositories containing 200 mg. of phenylbutazone have been found to produce clinical remission and sigmoidoscopic improvement in a large proportion of patients with proctitis, either primary non-specific or secondary. In the case of secondary proctitis, the primary disease was given appropriate treatment before employing suppositories for the proctitis.

Even better results were obtained with "combined" suppositories in which prednisolone and (in some cases) "protargol" were also included. Such "combined" suppositories brought about improvement in some patients who failed to improve with suppositories containing phenylbutazone alone.

I am grateful to the "Köbányai Gyógyszerárugyár," Budapest, for supplying the pure phenylbutazone as well as prednisolone.

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ACUTE ARSENICAL POISONING DUE TO ACETARSOL PESSARIES

BY

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Packing the vagina with acetarsol pessaries is sometimes recommended for resistant cases of trichomonal vaginitis. The danger of this method is illustrated by the following case (reported briefly in the *British Medical Journal* of July 16, 1960, p. 242).

A healthy married woman of 28 complained of vaginal discharge due to infection with *Trichomonas vaginalis*. She had not been pregnant, nor had she any serious illness. In January and February, 1958, she was treated for eight weeks with acetarsol 4-gr. (0.26-g.) pessaries, one night and morning for four weeks and then two each night for four weeks. Because the infection persisted and she complained of some local irritation, "penotrane" and then nystatin pessaries were given with lactic-acid douches. Nine months later (April, 1959) she returned to hospital and was treated with penotrane pessaries for a month and acetarsol 4-gr. (0.26-g.) pessaries two nightly for four months. In January, 1960, she was again treated, with "pruvagol" pessaries, but without improvement.

She was admitted to hospital, and on April 6 her vagina was packed, under general anaesthesia, with 18 acetarsol pessaries (total dose 72 gr.—4.67 g.). The next day she complained of nausea and vomited several times. As this was thought to be due to the anaesthetic she was given chlorpromazine hydrochloride ("largactil") 25 mg. On April 8 12 acetarsol pessaries (48 gr.—3.1 g.) were inserted into the vagina without anaesthesia. Nausea persisted and her temperature was 99° F. (37.2° C.). On April 9 she was restless and at midday had a generalized epileptiform fit, after which she was drowsy and disorientated. She appeared dehydrated; her pulse was 116 a minute, blood-pressure 110/70 mm. Hg, and temperature 100° F. (37.8° C.). There were no abnormal physical signs in the central nervous system: she was able to move all her limbs, the pupils reacted to light, and the fundi appeared normal; her jerks

were present and plantar reflexes were flexor. Her vagina was washed out, but it was empty. Ten hours after the first fit a second occurred, and so she was transferred to another hospital. On arrival there she was unconscious but responded to painful stimuli. The cerebrospinal fluid was clear and under normal pressure; it contained 24 lymphocytes per c.mm., a few red cells, and 75 mg. of protein per 100 ml. Blood investigations were as follows: haemoglobin, 14 g./100 ml.; white cells, 11,000/c.mm.; P.C.V., 36%; electrolytes: Na 132, K 4.5, and Cl 94 mEq/l.; alkali reserve, 9 mEq/l.; blood urea, 181 mg./100 ml.

A third fit occurred at 3.45 a.m. on April 10, 16 hours after the first one. She was given 10 ml. of paraldehyde by intramuscular injection and 4 ml. of dimercaprol in the next 14 hours. Later an intravenous drip infusion of 4.3% dextrose and 1/5 N saline was given. At 10.30 a.m. several more fits occurred, her coma gradually deepened, and she died at 6 p.m.

Post-mortem Examination (48 Hours After Death)

The deceased was of average build and adequately nourished. There was no evidence of any purpuric or erythematous rash and no evidence of haemorrhage. All the organs were congested and the brain substance showed moistness with some dilatation of the small vessels, but no evidence, macroscopically or histologically, of haemorrhagic encephalitis.

The stomach contained some bile-stained mucus, its lining was pale, and the smaller vessels were prominent. There was no visible inflammation anywhere in the intestines, and the large intestine contained some partly fluid faeces only.

Both kidneys showed a pale moist swollen cortex, the bladder was empty, the uterus and adnexae were entirely normal in size and appearance, and the cervix was healthy. There was no evidence of any ulceration or inflammatory change in the vagina, the mucosa appearing quite intact, but an acute vulvitis was present.

Microscopically the kidneys showed evidence of widespread tubular damage not localized to any particular area, with fresh blood casts in the tubules. The liver showed no evidence of necrosis, being healthy.

Analysis (Forensic Laboratories, Scotland Yard).—The liver was found to contain arsenic amounting to 0.3 gr. (20 mg.) (16 parts/million) as arsenious oxide, and it was calculated that this would indicate the equivalent of about 6 tablets of acetarsol, 4-gr. size, present in the whole body.

(To exclude acute porphyria as a cause of death in this case porphyrin estimation was carried out by Professor Rimington. The intestinal contents contained 43.8 μg./g. dried weight of coproporphyrin and 29.7 μg./g. dried weight of protoporphyrin. This result suggests a relatively small increase in coproporphyrin. It is known, however, that in cases of poisoning, among which arsenic is an example, the level of porphyrin may be slightly raised.)

Discussion

Acetarsol in the form of "stovarsol" or "S.V.C." pessaries is a recognized form of treatment in primary and resistant cases of trichomonal infection of the vagina. In the hospital concerned it has been carried out on numerous occasions without producing any serious untoward effects.

Serious skin reactions of any kind have rarely been reported to follow the widespread use of acetarsol for trichomonal infection, although minor reactions are well recognized (Campbell, 1937; Long, 1937; Kesten, 1938; Prosser-Thomas, 1948; Doyle, 1952; Peck, 1954).

There are even fewer reports of serious systemic reactions. Crosswell (1951) described the case of a patient developing rigors, facial oedema, a widespread morbilliform rash, and subsequently jaundice within a week of commencing treatment with acetarsol pessaries; dimercaprol was almost immediately effective. Liver-function tests indicated an obstructive lesion. Crosswell suggested that in the absence of liver-cell damage the bile becomes plugged in the capillaries due to an exudative reaction in adjacent tissues. Thompson and Marshall (1958) had a similar case of a woman who used two acetarsol pessaries at the twenty-second week of her third pregnancy; four weeks later she inserted six more pessaries—two each night for three nights. She developed rigors, prostration, gross oedema of the hands and face, and urticarial weals on the trunk. A week later she was deeply jaundiced; and tests showed that the lesion was obstructive. Antihistamine drugs and prednisone were given and she recovered, but the foetus died *in utero* and was born macerated. White (1956) reported the case of a woman who was admitted to hospital in a state of general collapse and mental confusion complaining of severe abdominal pain and a generalized erythematous rash. For three weeks before admission she had been treating a vaginal discharge with acetarsol, two 4-gr. (0.26-g.) pessaries night and morning. She was treated with cortisone, adrenaline, and intravenous fluids and recovered. In Worms's (1939) case encephalitis ensued when treatment with only one pessary was recommenced three months after the original course.

Brouardel (1902) mentions a man who murdered three women with inorganic arsenic (arsenious acid), introducing it into the vagina, in "boulettes de farine." From the evidence available on the absorption of pentavalent arsenicals from the intestinal tract there is no reason why it should not be absorbed from any mucous membrane if given in suitable quantities, and especially if the mucous membrane was inflamed or abraded; but in the case reported here, there was no evidence at necropsy of any vaginal mucosal abnormality. We are now investigating the arsenical content of blood, hair, and nails in patients who are being treated with acetarsol pessaries given daily.

The quantity of arsenic in the liver of this case, while not very great, is consistent with death from acute poisoning. By comparison, amounts found in the liver in well-known cases (as reported by Willcox, 1922) of arsenical poisoning are as follows: Maybrick, 0.3 gr. (20 mg.); the three Binghams, 1.1, 0.5, and 1 gr. (71, 32, and 65 mg.) respectively; Seddon, 0.17 gr. (11 mg.); Greenwood, 0.13 gr. (8 mg.). Larger amounts were found in the case of Radford, 2.75 gr. (178 mg.), and of Roberts, 1.75 gr. (113 mg.). In Egypt, where arsenical poisoning is commonplace, 3–5 parts per million are regarded as normal amounts. One must bear in mind that pentavalent arsenic (acetarsol) was administered in the present case, as experimentally it has been shown that excretion after intravenous injection in rats was most rapid in the case of the pentavalent compounds and slower with the trivalent group: also the toxicity of the trivalent arsenicals was greater than that of the pentavalent ones (Voegtlin and Thompson, 1922); so it may be that the toxicity of arsenicals is determined by the rate of excretion. After injection the pentavalent forms are to a large extent excreted before becoming fixed in tissues, and it is also probable that the pentavalent forms are reduced to the trivalent forms before exerting a marked toxic effect. Little work has been done on the absorption and excretion of acetarsol itself.

Reasonable proof that death was due in this case to arsenical poisoning appears to be present: first, there is

the known administration of arsenic (32 gr.—2.079 g.); second, symptoms known to be caused by arsenic were observed before death; and, finally, enough arsenic was found in the liver to account for death. In this connexion it is important to differentiate between examples of arsenical encephalitis following acetarsol administration and acute arsenical poisoning as described here. Although clinically there may be few distinguishing features, post-mortem findings, and in particular toxicological analysis, will readily provide the answer. Encephalitis may result from very small amounts of organic arsenical—for example, intravenous arsphenamine—but acute poisoning must be related to the amount ingested and may have medico-legal significance.

Summary and Conclusions

A fatal case of acute arsenical poisoning due to acetarsol vaginal pessaries is reported.

The treatment of vaginitis due to infection with *Trichomonas vaginalis* is often satisfactorily and safely carried out with acetarsol (stovarsol or S.V.C.) pessaries. Nevertheless, there is a very small risk of a mild skin reaction, and if treatment is continued the reaction may be severe and generalized. Such reactions may occur in the course of prolonged treatment or they may arise when treatment is recommended after a previous sensitizing dose. Jaundice or haemorrhagic encephalitis may also occur as a sensitivity response to organic arsenicals.

There is evidence that arsenic was absorbed from the vagina in the present case, and in theory either acute arsenical poisoning or haemorrhagic encephalitis could have followed. The distinction is important because the mechanism of production is quite different. Arsenical encephalopathy is not necessarily related to the amount of arsenic present, while acute arsenical poisoning is directly dependent on the amount of the drug that is absorbed. In fact, no such encephalitis was found, and there was enough arsenic in the liver to show that death was due to direct arsenical poisoning. This occurred as the result of packing the vagina on two out of three days with a total of 30 acetarsol pessaries. Such intensive treatment is sometimes recommended for resistant cases, but the presence of a vaginitis almost certainly increases the absorption, and in our opinion the method should be abandoned.

Our thanks are due to Dr. Dudley Hart, who took over the medical treatment of the patient when she was transferred, and to Dr. G. Thurston, H.M. Coroner for West London, for the post-mortem report.

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A *Bibliography of Directories of Sources of Information*, a booklet of 22 pages, has been compiled on behalf of the International Federation for Documentation, 7 Hofweg, The Hague. Netherlands. Inquiries should be addressed to the Federation at that address.

MYOGLOBINURIA AND SEA-SNAKE-BITE POISONING*

BY

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The clinical paradox of trismus yet paresis elsewhere originally stimulated investigations of sea-snake-bite poisoning (Reid, 1956a). Experimentally, sea-snake venom is feebly haemolytic: theoretically, a dose of venom sufficient to cause haemolysis should inevitably be fatal. Yet patients survived despite apparent haemoglobinuria. In these survivors, moreover, there was no evidence of excessive haemolysis. These anomalies were resolved in 1957 when it was realized that the urinary pigment was myoglobin, not haemoglobin. The purpose of this paper is to present case records and clinical investigations of patients selected as elucidating the pathogenesis of sea-snake-bite toxaemia.

Material

During 1957–9 38 patients with sea-snake-bite were personally observed in hospitals. The sea-snake was reliably recognized in 25 cases (23 were in fishing folk); in four subjects—all bathers—typical toxaemia followed; and the remaining nine patients ("probable cases") were bitten in the sea, felt no local pain after the incident (thereby excluding fish-stings), and had bite-marks compatible with those of a sea-snake. In this selected series of 38 victims serious poisoning followed in only nine cases (five fatal, three severe, one moderate). Trivial toxaemia resulted in two instances and no poisoning followed 27 bites (18 unequivocal, 9 "probable" as defined above). The following case records and investigations are representative of the minority developing poisoning.

Case 1

An Englishman aged 32 was bitten in the left calf while bathing at 4 p.m. on September 2, 1957. The first symptom was slight giddiness at 4.25 p.m. On reaching hospital at 4.30 p.m. the back of his neck felt stiff and ached, particularly on moving his head. At 4.35 his tongue felt stiff and was slightly swollen, there was some pain on swallowing, and all four limbs were stiff on moving "as if I had taken a lot of exercise." At this time the admission doctor found the B.P. 140/92. Dr. C. P. Cheah, who had examined the patient for life insurance on September 8, 1955, kindly informed me subsequently that the B.P. was then 125/68. At 6.30 p.m. the B.P. was 120/100, and on the left calf were multiple pin-point marks which could only have been made by at least two bites.

His pupils were equal, not unduly dilated, and reacted briskly to light. Abdominal reflexes were present, plantar responses flexor. He was unable to look to the left, otherwise eye movement was normal. He could clench his jaws strongly and open them 35 mm. (between teeth edges). Showing his teeth or grinning was difficult owing to stiffness of his face, but there was no asymmetry of movement. Palate movement and coughing appeared normal, but the latter caused pain in the abdomen and lower ribs. Swallowing of fluids was painful although not otherwise difficult. Hearing a watch and appreciation of light touch, pinprick, joint movement, and vibration were normal. There was no nystagmus. He could lift his head off the bed against strong pressure, but turning it to either side was painful. He could

*Based partly on a thesis for the degree of M.D. in the University of Edinburgh.

sit up spontaneously (although this made him giddy) and could lift all four limbs off the bed. They were tender on pressure but not swollen or unduly hard. Active or passive flexion was extremely painful—much more so than pressure. He described this pain as "cramping" and groaned with the severity. Muscle tone was difficult to judge in the circumstances but was probably normal. Tendon reflexes were brisk.

At 7.30 p.m. he was unable to move his eyes in either lateral direction. Vertical movement was about 50% normal. Jaw-opening was 33 mm. At 9.30 p.m. he felt "lousy." Both pupils were dilated but reacted to light. They did not constrict when he attempted to accommodate—he was unable to turn his eyes inwards for this and saw double when my finger was brought within 2 ft. (60 cm.) or less. Visual acuity (reading newsprint) was normal.

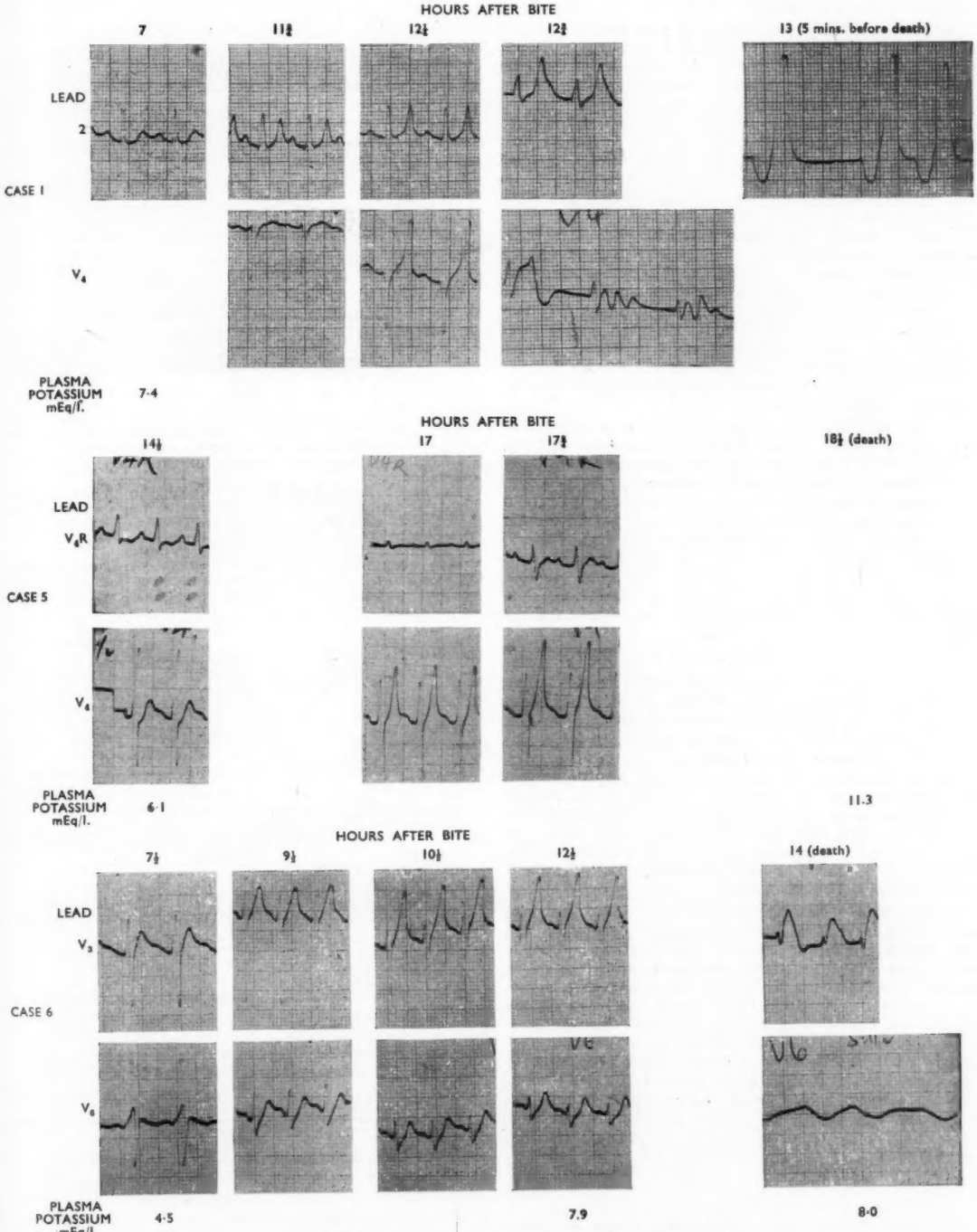

FIG. 1.—Electrocardiograms showing progressive hyperkalaemia.

Maximal jaw-opening was now 23 mm. He could not protrude his tongue beyond the teeth or lift his head off the bed, and could raise the heels and right arm off for only a few seconds. The left arm was splinted for the intravenous drip of 20% glucose (1 litre was given rapidly between 7.30 and 9 p.m.). At 10 p.m. his pupils were equally dilated, but the right one no longer reacted to light. The left reacted slowly. Ptosis was now evident. He tried to swallow water but had great difficulty with it. Passive movement of limbs continued to be very painful.

At 11 p.m. the nurse attempted to pass a Ryle tube and he vomited. I immediately turned him in to the prone position and then lifted the end of the bed on to high blocks. No vomit was inhaled. Coughing was feeble but respiration appeared satisfactory. At 11.15 p.m. the first electrocardiogram (E.C.G.) was taken (see Fig. 1). Increased sweating was noted, B.P. was 160/120, breathing had become shallow, and breath sounds were faint. At 11.45 p.m. he was comatose, fingers cyanosed, B.P. 180/125. It was therefore decided to do a tracheostomy and give intermittent positive-pressure artificial respiration (I.P.P.R.) with an Oxford Radcliffe machine. The anaesthetist, Dr. L. T. Scott, was surprised how strongly he had to hold the patient's arm to give the atropine and thiopentone injections. When I.P.P.R. was started it was soon apparent that he was "fighting the machine." We were naturally reluctant to give D-tubocurarine in view of sea-snake venom itself having a neuromuscular blocking action in animals, but his condition was desperate, and therefore at 1 a.m. on September 3 30 mg. of D-tubocurarine was injected intravenously. Cyanosis rapidly disappeared.

For the next two hours a good colour and breath sounds with minute-volume 10.5–11.5 litres continued, yet the B.P. remained 150–170/120–130. At times both legs were moving slightly and his arms had to be held down. At 3.40 a.m. he became cyanosed, no pulse was felt, and the B.P. could not be recorded. The second E.C.G., at 3.45 a.m., showed hyperkalaemic T waves and widening of the angle between S and ST segment (see Fig. 1). An intravenous drip of noradrenaline was started at 4 a.m., but there was no improvement. At 5.05 a.m. the heart could no longer be heard and no E.C.G. record could be obtained—13 hours after the bite.

Case 2

At 5.15 p.m. on June 13, 1958, a 10-year-old Indian schoolboy was having a swimming race when his right foot touched the mud and he felt a prick. He thought it was a nail and reached down to remove it, but instead felt a sea-snake. He returned to school and started a game of marbles, which entailed frequent bending. At 5.45 p.m. he noticed increasing pains in both buttocks. At 5.55—on his way to hospital—the pains spread to his throat, neck, and hips. He walked 100 metres from the car to the admission office, and on arriving at 6 p.m. said he could not move his limbs. The back was also painful and any movement made the pains much worse. His mouth felt stiff.

On examination two fang marks 15 mm. apart were seen on the right instep. He was not sweating unduly; the B.P. was 110/85. He lay on his back with forearms and wrists flexed, legs straight. Power and tone were difficult to estimate because of the distress any active or passive movement produced. He could lift his head and limbs off the bed but was unable (or unwilling) to sit up. Passive movement, however, appeared to be resisted by powerful contraction in the opposer muscle groups. Progress thereafter is summarized in Fig. 2. The blood-pressure remained normal until 15 minutes before death. Respiratory failure was counteracted by I.P.N.P.R. (positive-negative pressure) and hyperkalaemia by rapid infusion of glucose and calcium, yet the patient died 14¼ hours after the bite.

Case 3

A Chinese mechanic aged 17 was bitten on the left lower leg at 5.45 p.m. on May 14, 1957, while bathing. Frontal headache started at 6.30; pains in the throat, right shoulder, and chest, with thirst and increased sweating, at 6.45. At hospital, at 7 p.m., he had difficulty in raising his limbs from the stretcher; sweating was profuse, and B.P. 140/90. At 9.15 p.m. he was unable to sit up without help but could lift his head against resistance. Limb power was objectively

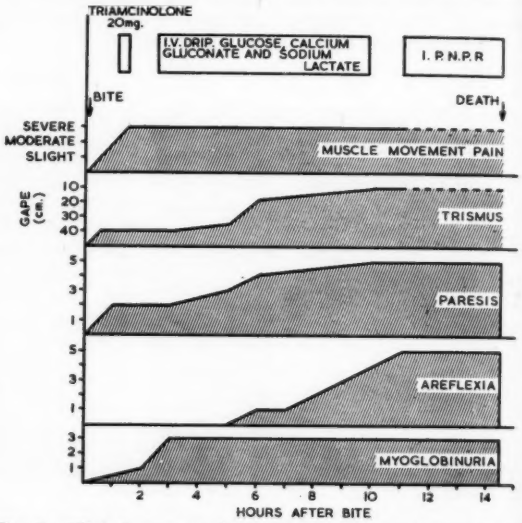

FIG. 2.—Clinical course to death (Case 2). Paresis follows in the wake of muscle-movement pain. Death occurred despite adequate artificial respiration and prevention of hyperkalaemia.

I.P.N.P.R.=Intermittent positive/negative-pressure artificial respiration.

Paresis.—5=respiratory failure; 4=unable to lift one or more limbs; 3=unable to lift head; 2=unable to sit up spontaneously; 1=objective weakness less than 2.

Areflexia.—5=7–8 tendon reflexes absent; 4=5–6 absent; 3=3–4 absent; 2=1–2 absent; 1=present but weak.

Myoglobinuria.—3=dark brown, red, or black, spectroscopically positive; 2=light brown or dark yellow, spectroscopically positive; 1=benzidine-positive, spectroscopically negative.

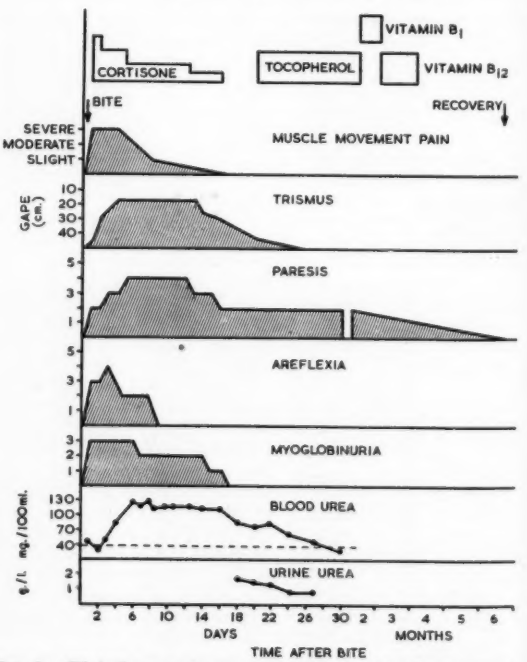

FIG. 3.—Clinical course to recovery (Case 3). Muscle-movement pains recede before paresis. Tendon reflexes recover quickly. Raised blood urea with low urinary urea reflects renal damage. (Notation as in Fig. 2.)

normal despite his claim that he "could not move." All limbs were held flexed, and passive movement was disliked owing to the pain it caused. Muscles were tender on pressure, but this did not cause as much distress as passive movement. Tendon reflexes were present. Movement of eyes, face, tongue (which was moist), palate, and shoulders was full. On the lower left leg fang marks 8.5 mm. apart could be easily distinguished from two maxillary and four pterygoid teeth marks. The remaining findings were not abnormal.

Further progress is illustrated in Fig. 3. At 9 a.m. on May 15 muscle pains and tenderness were more severe in the neck, shoulders, and thighs; thirst continued. At 5 p.m. there was objective weakness of arm abduction but no other change in muscle power. Arm-jerks were absent, knee- and ankle-jerks present. On May 16 muscle pains were worse. Objectively, muscle power was now significantly diminished in the neck, back, and proximal limbs. Neostigmine 2 mg. was injected intravenously, but no benefit was observed. On May 17 the shoulder, arm, and thigh muscles were weaker. On May 18 pains and tenderness started to recede but paresis had increased. Both scapulae showed "winging," pectorals were weak, and hand-grip was feeble. Knee-jerks were now absent and ankle-jerks very sluggish.

During the second week paresis in proximal limbs, trunk, and neck remained essentially the same, but further loss of power occurred in forearm and hand muscles. By the middle of the second week tendon reflexes were all brisk except the ankle-jerks. The urine still contained myoglobin but the colour was lighter. From the start of the third week there was a progressive improvement in power and a recession of trismus and myoglobinuria (see Fig. 3). He was able to lift his head off the bed and could sit up by rolling on to his right side and helping himself up with his right arm like a patient with muscular dystrophy. By the sixth week lower-limb power appeared objectively normal. Arm abduction, forearm extension, and hand flexion were weaker on the left than on the right side. He could sit up spontaneously 10 weeks after the bite. By mid-September press-ups had become normal compared with a control patient of his own age and build: hand-grip was still weaker on the left than on the right. In November he had fully recovered.

In the first week after the bite the B.P. was 120/70–80, but during the next 10 days, when there was non-oliguric renal insufficiency (see Fig. 3), mild hypertension (140–145/90–100) was present. Thereafter the B.P. returned to normal. There was no clinical or radiological evidence of any cardiac or lung lesions, but there were E.C.G. changes. Dominant R waves developed in right chest leads, and T waves rose from 4 mm. in height 15 hours after the bite to 14 mm. three weeks later, although serum potassium on the 22nd day—the only estimation made—was 4.6 mEq/l. Blood urea at this stage was already falling.

Case 4

An Indian boy aged 15 was wading ashore from his boat at 9 a.m. on May 20, 1958, when he was bitten on the inside of his right ankle. When he reached the hospital at 10.30 a.m. he felt pains in the right leg, elbow, and neck. Physical examination was negative. He was advised to drink as much fluid as he could manage. The third urine specimen (six hours after the bite) was positive for occult blood and the next two (9 and 11 hours after) were strongly positive. The sixth (17 hours after) was still positive but subsequent specimens were negative. The limb and neck pains continued until May 21.

Investigations

Haematology.—Leucocytosis was present in all the subjects in whom poisoning was serious, counts exceeding 20,000 being confined to fatal cases; the degree and duration correlated approximately with the severity of the toxaemia. Eosinophils were not increased. No evidence of abnormal haemolysis or coagulation defect was found. Reticulocytes, platelets, saline fragility, serum bilirubin, urinary urobilinogen, bleeding-time, coagulation time, one-stage prothrombin time, direct Coombs, Schumm's, Donath–Landsteiner, and Kahn tests were always normal. The erythrocyte sedimentation rate was raised in Case 3 and normal in another severe case.

Biochemistry.—In each of the nine serious cases myoglobinuria was identified by comparison spectroscopy, the difference from a control urine with haemoglobin being unequivocal. The earliest visible change in the urine was a dusky yellow colour, when protein tests and the benzidine or occult blood test would be positive but spectroscopy negative. Urine of this nature was passed six hours after the bite in Case 1, eight hours after in Case 4. Within an hour or less the urine became brown or red and was then spectroscopically positive—in Case 2 this type of urine was passed three hours after the bite. Seven victims did not pass urine until 7–22 hours after the bite, when the colour was already dark brown or red. The patient who survived the most severe poisoning (Case 3) excreted roughly 18 g. of myoglobin during the first 17 days after his bite, thus losing about one-tenth of his total myoglobin. In another severe case the subject lost about 16 g. in a week. An important pathogenic observation in the two trivial cases was the occurrence of myoglobinuria even though poisoning was so minimal that paresis could not be detected. The urine reaction might be acid or alkaline. Micropsy showed granular casts if pigment or protein was present, but significant red blood cells were absent. Although oliguria was not a feature in Case 3, the findings suggested renal damage (see Fig. 1). Follow-up studies indicated that this might be permanent in some cases.

Progressive hyperkalaemia occurred in Cases 1, 5, and 6 (see Fig. 1). Plasma potassium and blood creatine and creatinine remained normal in Case 2 up to three and a half hours before death. In Case 5 blood creatine rose from 0.4 (14½ hours after the bite) to 2.7 mg./100 ml. at death (18½ hours after the bite). Creatinine remained normal. Urine creatine totalled 59 mg., creatinine 250 mg., in 318 ml., obtained four hours before and at death (not estimated in Case 2). Plasma sodium and blood urea remained within normal limits in Cases 2, 5, and 6, but in Case 1 blood urea rose from 37 mg./100 ml. seven hours after the bite to 70 mg. at death.

Plasma protein electrophoresis suggested liver damage in one severe case (not done in others), but at follow-up studies of patients with severe or moderate poisoning liver function as judged by bromsulphalein clearance test was normal. Lumber puncture in a case previously recorded (Reid, 1956b) revealed normal cerebrospinal fluid.

Electrocardiography.—Serial records with standard, unipolar, and eight chest leads (V_4R–V_6) were taken throughout toxaemia from 9 of the 11 patients. In Case 2 (up to two hours before death), the single moderate case, and one of the two trivial cases, records remained normal. In Cases 1, 5, and 6 signs of progressively severe hyperkalaemia developed (see Fig. 1). In Case 5 and all three patients with severe poisoning, monophasic or dominant R waves were present in V_4R. In Case 3 and one of the other severe cases R was also dominant in V_3R and V_1. In follow-up

studies the pattern of right ventricular dominance persisted unchanged in the latter case. However, this 11-year-old boy was an asthmatic and therefore the significance of the E.C.G. records in relation to sea-snake poisoning is uncertain. In Case 3 there was some regression of the pattern after his discharge. One year after the bite R equalled S in V_1 and V_3R, and 16 months afterwards S exceeded R in V_4R–V_1. But ventricular activation time in V_1 remained prolonged at 0.05 second.

Electrodiagnosis.—In the three severe cases there was no qualitative change in serial tests with faradic and galvanic stimulation. Contraction in response to faradic current remained brisk although diminished in amplitude—there was no reaction of degeneration. Recovery of normal amplitude was rapid (two to three weeks). Apparatus for intensity-duration curves and electromyography was not available.

Neostigmine Test.—Because experimental work in animals suggested that sea-snake venom acts by blocking the neuromuscular junction, neostigmine was given intravenously in a case already reported (Reid, 1956b) and in the three severe cases, but no improvement was observed.

Muscle Biopsy.—In Case 3 biopsy of the left deltoid muscle on the third day after the bite, when muscle-movement pains were maximum, showed necrosis of 30% of the fibres. Right deltoid biopsy six months later showed fine scarring (Marsden and Reid, 1961).

Radiology.—Chest radiographs were taken in all except fatal cases at varying times after the bite during the toxaemia and at follow-up studies. No abnormality of the heart shadow or lung fields was observed except for increased markings in the asthmatic victim. Dr. J. F. Goodwin kindly confirmed the absence of radiological changes suggesting pulmonary hypertension (Goodwin, 1958). Intravenous pyelograms were normal in Case 3 and the asthmatic patient.

Discussion

Experimentally, Barnes and Trueta (1941) found that cobra venom, because of its low molecular weight (under 5,000), was rapidly absorbed through the capillaries direct into the blood-stream. In contrast, venoms with higher molecular weights were absorbed more slowly via the lymphatics. In human victims of poisoning from sea-snake-bite the latent period of 30–60 minutes has been remarkably constant irrespective of the site of the bite or of the venom dose as judged by subsequent progress. J. E. Carey (personal communication, 1959) considered the molecular weight of *E. schistosa* venom to be 9,000 or under. These findings suggest that absorption of sea-snake venom in human victims is a process of diffusing up the interstitial tissues either into capillaries direct or via lymphatics and thoracic duct, through the pulmonary circuit, and thence into the systemic circulation. From here the venom affects skeletal muscles according to blood flow and anatomical propinquity to the pump. Thus it is that throat, neck, back, or proximal limb muscles are the first to show the characteristic stiffness and muscle-movement pains.

Hitherto it has been assumed from animal experiments that sea-snake venom is predominantly neurotoxic to human victims At necropsy on human patients, no histological abnormalities have been found in the nervous system—but this is also the case in tetanus toxaemia, and the primary site of action of tetanus toxin on nervous tissue is not disputed. Clinically in human patients with sea-snake poisoning the outstanding early feature is muscle-movement pain. However, such pains are also common in myalgic encephalomyelitis and the preparalytic phase of poliomyelitis. It might be argued that the muscle-movement pains are merely early signs of neurological involvement. Undoubtedly paresis and areflexia eventually ensue. Might the myoglobinuria not be secondary to a neuropathic paresis? Personally I am convinced that in human subjects sea-snake venom acts primarily on skeletal-muscle cells for the following clinical reasons:

1. Muscle-movement pains precede paresis by several hours in rapidly fatal cases or by as long as 24 hours in severe poisoning.

2. Much of the paresis is apparent rather than real, as shown by objectively normal limb power in Case 3 when the patient said he "could not move," also by various activities late in the paresis of fatal cases.

3. Trismus in tetanus is neurogenic, but it differs strikingly from trismus in sea-snake toxaemia. The latter can be reduced by sustained pressure on the lower jaw—this does not increase the gape in tetanus at all. Secondly, the jaw-jerk is very brisk in tetanus, and absent or sluggish in sea-snake poisoning. This suggests that the trismus and stiffness in limbs and trunk are due to the splinting reaction of intact muscle cells protecting injured cells against further damage by stretching.

4. No fibrillation or muscle fasciculation is seen at any stage.

5. In severe cases there is no qualitative change in response to faradic and galvanic stimulation—this is typical of a myopathic lesion (Walton and Adams, 1958).

6. Myglobinuria may be apparent before paresis, and is present in minimal poisoning with no detectable paresis.

7. There is no evidence of sensory, cerebellar, or meningeal involvement and, except in terminal toxaemia, no mental or higher cerebral upset.

8. Necropsies show widespread myonecrosis even when victims die only 13 or 14½ hours after the bite (Marsden and Reid, 1961).

The flaccid paresis which follows later can be explained by progressively increasing muscle damage. Absent tendon reflexes have been recorded in purely myopathic conditions such as polymyositis (Walton and Adams, 1958) and do not necessarily indicate a neural lesion. If, however, the loss of tendon reflexes and their rapid return in some cases do reflect a neurotoxic as well as myotoxin action, the absence of sensory change, fasciculation, and wasting suggest a block at the myoneural junction. This would be due to failure of the end-plate to respond to the transmitter (Lilienthal and Zierler, 1957) rather than to a curariform type of block, since neostigmine is quite ineffective.

There is no pain in the joints and, unlike the muscles, they are not tender. Minimal joint movement not entailing significant change in muscle length is painless: once myalgia has resolved, full joint movement is painless. These facts and the myoglobinuria exclude a primary joint lesion.

In contrast to extensive skeletal myonecrosis, no histological abnormality is found in smooth muscle or the myocardium. However, the E.C.G. pattern of right ventricular dominance suggests some change in the myocardium or pulmonary vessels. There is no clinical, radiological, or histological evidence of pulmonary vasoconstriction, and systemic hypertension in the absence of respiratory failure is exceptional.

Gailani, Danowski, and Fisher (1958) found similar E.C.G. changes in patients with muscular dystrophy, and they excluded pulmonary hypertension or right heart enlargement by cardiac catheterization. They attributed the changes to conduction defect in the myocardium. This may be the explanation of the abnormal E.C.G.s in sea-snake poisoning. Yet it is peculiar that a toxaemic conduction defect should persist as long as one and a half years after the bite. In Case 1 there was persistent systemic hypertension (known to have been absent prior to the bite) right from the start of the toxaemia. Early hypertension was not present in the other patients, so a direct venom effect on smooth muscle of arterioles seems unlikely. Could it have been a renal pressor factor secondary to kidney damage by the venom? There has been histological evidence of kidney damage in most patients coming to necropsy. Clinically, shock is not a feature—hypotension was not observed except within an hour or two of death.

Although serum bilirubin remained normal, electrophoresis of plasma proteins suggested liver dysfunction. Kidneys showed tubular necrosis in three necropsies (Marsden and Reid, 1961), and in Case 3 the raised blood urea with low urinary urea and "fixed" specific gravity indicated serious renal damage although the urine volume was normal. The constant thirst, with a moist tongue, is attributed to cellular dehydration or increased osmolarity of extracellular fluid, although it may be due to a direct biochemical effect on the thirst centre (Fourman and Leeson, 1959). As the venom disrupts muscle cells to the extent of releasing myoglobin there must be a concomitant escape of potassium, magnesium, and other substances into the interstitial tissues. Hyperkalaemia was a major factor in three deaths. Potassium and magnesium upset at the end-plate might be further components in the late-developing paresis.

Myoglobinuria is easily overlooked or mistaken for haemoglobinuria. It is a sign of skeletal-muscle damage, probably involving myonecrosis, which may be caused by a variety of insults, including: (1) Trauma, which may be physical, such as crush injuries (Minami, 1923; Bywaters and Beall, 1941), severe assault (de Langen, 1946), or status epilepticus (Iversen, 1948); electrical (Fischer and Rossier, 1947); or by burns (Campbell and Ezrin, 1954). (2) Inflammatory, due to bacterial infections, such as typhoid and gas-gangrene, leptospiral (Adams, Denny-Brown, and Pearson, 1953) and viral infections (Lépine, Desse, Sautter, 1952), and polymyositis (Günthur, 1924; Paul, 1924; Walton and Adams, 1958). (3) Endocrine, such as myxoedema (Marshall and McCaughey, 1956). (4) Ischaemic (Bywaters and Stead, 1945; Elek and Anderson, 1953). (5) Familial (Louw and Nielsen, 1944; Hed, 1955). (6) Toxic causes, which include Haff disease (Hed, 1955), alcohol and barbiturates (Fahlgren, Hed, and Lundmark, 1957), carbon monoxide (Loughridge, Leader, and Bowen, 1958), and, now, sea-snake poisoning. (7) Idiopathic myoglobinuria with or without dystrophy (Pearson, Beck, and Blahd, 1957).

The similarities of sea-snake poisoning to Haff disease are striking—muscle-movement pain and a feeling of stiffness, sweating, thirst, leucocytosis, and a proneness to acute renal failure. The name comes from the sea inlet Frisches Haff, where epidemics occurred in 1924–5, 1932–3, and 1940. Berlin (1948) observed a small outbreak in 1942–3 around Lake Yusen just south of Mariestad, in Sweden. The great majority of victims were fishermen (but sea-snakes cannot be incriminated as they have never been recorded from these regions). The cause was never elucidated, although Berlin thought it might be an aneurine-inactivating factor similar to that producing Chastek paralysis in foxes. Because of this theory, two patients with severe sea-snake poisoning were given parenteral vitamins, but no convincing improvement resulted.

To summarize pathogenesis so far as clinical features assist elucidation, the tissue primarily attacked by sea-snake venom in human victims is skeletal muscle. The attack is generalized throughout the body, but certain areas such as the neck, trunk, and proximal limbs bear the brunt. There is electrocardiographic evidence that the myocardium may be affected. Kidneys and liver are usually involved and nerve tissues may possibly be implicated later, but it is uncertain whether these are direct effects of the venom, due to secondary toxic metabolites, or caused by a combination of these factors.

Summary

Clinical observation indicates that sea-snake venom is primarily myotoxic to human victims. Generalized muscle-movement pains and myoglobinuria are the outstanding symptoms of poisoning. There is a close similarity to other syndromes with myoglobinuria, particularly Haff disease.

Death may result from respiratory failure (through skeletal-muscle damage, inhalation of vomit or secretions, and respiratory infection), hyperkalaemia, or acute renal failure. Even when these dangers are counteracted by treatment, death may occur.

In severe cases recovery may take up to six months and some of the clinical features resemble muscular dystrophy.

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PATHOLOGY OF SEA-SNAKE POISONING

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Sea-snake bite is an occupational hazard to fishermen in Asia (Reid and Lim, 1957), but the pathological lesions in man have not yet been properly described. In animals, Rogers (1903a, 1903b), Fraser and Elliot (1905), and Wright (1956) found a neurotoxic effect on the brain-stem and neuromuscular junctions. Kellaway, Cherry, and Williams (1932) considered that the venom of *Enhydrina schistosa* (Daudin) acted solely on the neuromuscular junction. Rogers (1903a), Nauck (1929), and Carey and Wright (1960) found little at necropsy. Lamb and Hunter (1907) injected *E. schistosa* venom subcutaneously into five monkeys and described degenerative changes in the central nervous system and peripheral nerves. In contrast, no histological abnormality was found in nerve tissue from two patients, although one did not die until three days after the bite (Reid, 1956a). Recent clinical observation has shown further discrepancies between the results of animal experiments and poisoning in human victims (Reid, 1961). Complementary to these clinical observations, we have found the chief pathological lesions to be in skeletal muscle, kidney, and liver. Our purpose is to describe these lesions and discuss some implications.

Material and Methods

This study is based on biopsy material from a patient who recovered from severe sea-snake poisoning and on the necropsy findings of seven patients. All patients, except Case 4, were personally observed during the toxaemia and at necropsy by one of us (H. A. R.). In Case 4 the clinical features and macroscopic findings at necropsy were personally confirmed with the doctor in charge. Pathological effects in Cases 7 and 8 have already been briefly described (Reid, 1956a), but, in view of the more recent findings, we have been able through the courtesy of Professor William Blackwood to review the histology in muscle and renal tissue. Case records of five subjects have been published elsewhere —Cases 1, 2, and 3 by Reid (1961, same case numbers); Case 7 by Reid (1956b); Case 8 by Reid (1956c, Case 3).

The constant high temperature (averaging 30° C.) and humidity of the Malayan climate is most unfavourable for the histological study of necropsy material, and particular efforts were made to combat this difficulty. The body was transferred to the mortuary refrigerator (temperature 9° C.) within 30 minutes of death in all cases except Case 4. The time between death and necropsy is shown in Table 1. Specimens for histology were immediately placed in formol-saline: in Cases 1 and 2 duplicate specimens were fixed in Bouin's fluid, and in Helly's fluid and alchohol in Case 3. Blocks were embedded in wax, and routine sections were cut and stained by haematoxylin and eosin. Sections of muscle were also stained by Masson's trichrome method and by phosphotungstic acid haematoxylin; other special stains were used as required.

Results

Findings are summarized in Tables I and II. Macroscopic changes are few, the most important being brown

TABLE I

Case No.	Hours Between Bite and Death	Hours Between Death and Necropsy	Macroscopic Findings (bladder contained brown or black urine in all cases)	Principal Histological Findings: Skeletal Muscles Examined with % Necrosis	Heart	Kidney	Liver	Lung	Other Organs
1	13	6	Few petechiae under liver capsules: liver pale	Deltoid 20%. Intercostal 30%. Diaphragm 33%	Normal	Congestion	Centrilobular degeneration. Portal round-cell infiltration	Patchy oedema	Brain-stem: normal
2	14½	2	Normal	See Table II	,,	Congested boundary zone	,, ,,	Small areas of collapse and emphysema	Parotid gland: normal. Lymph node: sinus catarrh. Thyroid: necrosis
3				Biopsy 3 days after bite: deltoid 30%. 6 months later: fine scarring					
4	25½	4½	Pale liver	Tongue 45%. Intercostal 65%. Biceps 33%. Quadriceps 35%	,,	Congested boundary zone	Hydropic degeneration parenchyma: Portal round-cell infiltration		Pancreas: normal. Bladder: chronic inflammation mucosa. Thyroid: normal
5	18½	7½	Normal	Eye. Lateral rectus 100%. Face 50%. Tongue 60%	Slight endocardial fibrosis	Congestion	Congestion. A few focal necroses. Portal polymorph infiltration	Small areas of collapse and emphysema	Oesophagus, stomach, bladder: chronic inflammation. Suprarenal: depletion lipoids cortex. Thyroid: normal
6	52	11	Right heart distended; purulent froth in main bronchi; kidneys bulged from capsule		Normal	Distal tubular necrosis	Centrilobular necrosis ¼–2/3 lobules	Bronchitis	
7	77	15	Scanty petechiae in lung fissures and epicardium; pale liver; brain congested	Quadriceps 55%	(Coronary sclerosis)*	(Distal tubular necrosis)†	(Centrilobular degeneration. Portal polymorph infiltration)*	(Congested)*	(Brain-stem, basal ganglion, sciatic nerve: normal)*
8	12 days	31	Petechiae and ecchymoses throughout viscera	Quadriceps 55%	Slight fibrosis	Distal tubular necrosis			

* Previously reported (Reid, 1956a). † Kindly confirmed by Professor J. H. Dible.

or black urine in the bladder. The liver may be pale. Colour and consistency of skeletal muscle are normal. Bite marks are inconspicuous and there are no visible changes in tissues immediately adjacent. Histological changes are as follows.

TABLE II.—*Widespread and Advanced Necroses in Case 2, Although the Patient Died Only 14½ Hours After the Bite*

Severity of Myonecrosis	Duration of Myonecrosis			
	Oldest. More than 70% Contracted	60% Contracted	40–50% Contracted	Most Recent. 25% or Less Contracted
Very severe; 70% or more fibres necrosed	Trapezius. Pharyngeal		Triceps. Biceps. Forearm flexor. Forearm extensor	
Severe; 50–70% fibres necrosed	Intercostal (upper)	Tongue. Intercostal (lower). Diaphragm. Gluteus maximus	Masseter	Quadriceps
Moderate; 45% necrosis			Pectoral	
Mild; 25% necrosis				Psoas. Gastrocnemius. Peroneus

Skeletal Muscle

There are widespread hyaline necroses in skeletal muscles. The toxin picks out individual muscle fibres, leaving a healthy fibre next to a necrosed one, and affects only one or more segments of varying length in a fibre, usually with an abrupt transition to normal muscle (see Fig. 1). The number of fibres with focal necroses varies from muscle to muscle: in the same patient there may be necroses in 20% or less of the fibres of one muscle while in another muscle every fibre shows necrosis (see Table II). The affected segment of a muscle fibre first becomes greatly swollen and the sarcoplasm undergoes coagulation necrosis. At this stage the nuclei and swollen myofibrils can still be distinguished, but the disks of the myofibrils soon lose their differential staining, and both nuclei and myofibrils disappear as they become fused into an amorphous hyaline mass. This necrotic material contracts, leaving an empty space beneath the sarcolemma, which remains intact although it may slightly collapse (see Fig. 2). Necrotic segments stain more intensely with acid dyes, but this is not conspicuous in routine sections and could easily be overlooked by casual or inexperienced observation. The myonecroses become very obvious with special stains. With Masson's trichome stain they appear bright red, while the sarcolemma is blue. The

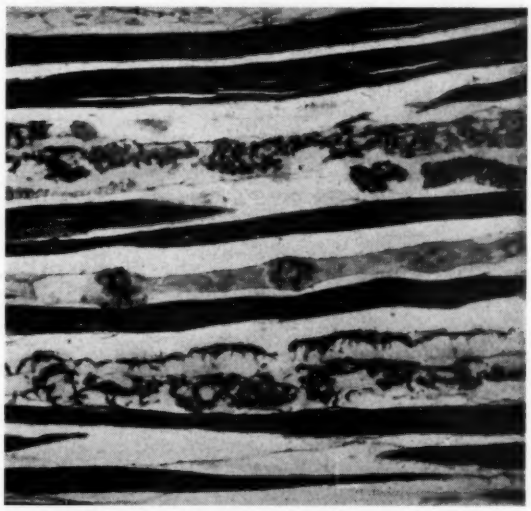

FIG. 2.—Later stage of myonecrosis with necrotic material contracted and tending to break up; the sarcolemma is still intact. (Phosphotungstic acid haematoxylin. ×110.)

picro-Mallory method stains them yellow; they are deep red with phosphotungstic acid haematoxylin and greenish with van Gieson's stain. Best's carmine stain shows a loss of glycogen from the necrosed segments.

Soluble products, notably myoglobin, enzymes, and electrolytes, are rapidly absorbed into the blood-stream. Insoluble necrotic fragments are phagocytosed by histiocytes and macrophages (see Fig. 3). Regeneration and repair begin one to two weeks after the bite with multiplication of surviving muscle nuclei (see Fig. 4). The muscle fibre is thus regenerated within its original sarcolemmal sheath and repair is remarkably complete, probably because very few muscle fibres are entirely necrosed. In Case 3, biopsy six months after the bite showed only a little fine scarring (see Fig. 5).

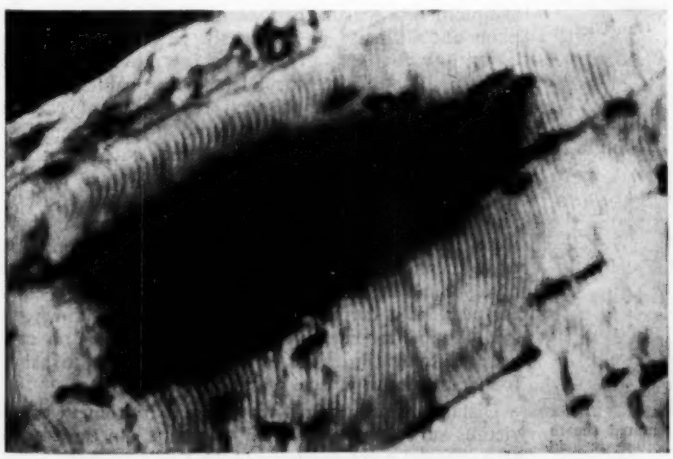

FIG. 1.—Early necrosis of a muscle fibre, showing swelling and abrupt transition to normal muscle. (van Gieson. ×400.)

Kidney

The earliest changes as shown by Cases 1, 2, 4, and 5, in which death occurred within 26 hours of the bite, are slight and entirely vascular. The whole kidney is engorged, but the boundary zone is intensely congested and stands out prominently. There are a few granular myoglobin casts in the tubules and there may be a little leakage of plasma and a few red cells from the congested glomeruli. Oedema, even of the boundary zone, is seldom marked and may be absent.

Distal tubular necrosis has been found in all three patients who survived for more than 48 hours after the bite. There is extensive necrosis of the epithelium of the loop of Henle, the second convoluted tubule, and the collecting tubules. Desquamated cells with granular and

amorphous debris fill the lumen and form casts in the distal and collecting tubules. Pigment giving a positive benzidine reaction is deposited in most of the casts, and even in some of the desquamated cells. The boundary zone is still intensely congested and the interstitial tissue is now oedematous, as well as showing both a diffuse and a focal cellular infiltration.

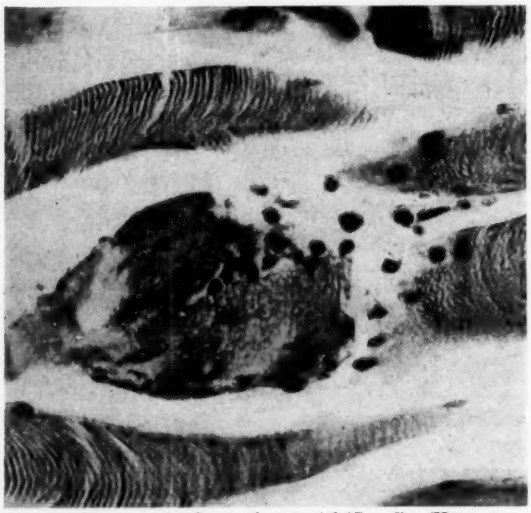

FIG. 3.—Phagocytosis of necrotic material (Case 8). (Haematoxylin and eosin. ×530.)

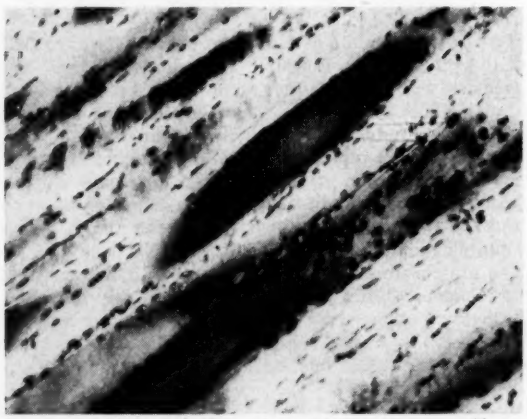

FIG. 4.—Multiplication of muscle nuclei (Case 8). (van Gieson. ×160.)

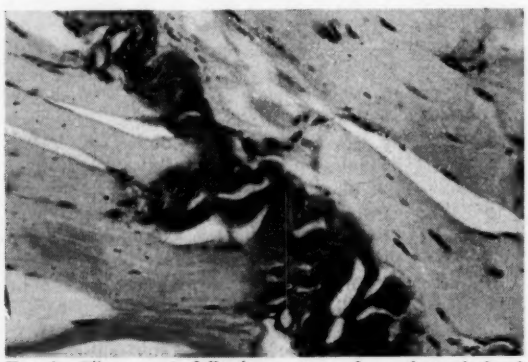

FIG. 5.—Fibrous scar following rupture of sarcolemmal sheath (Case 3: biopsy six months after bite). (Phosphotungstic acid haematoxylin. 140.)

The reactionary or healing stage is not often seen because victims usually die too quickly. Case 8 was our only example—the patient died 12 days after the bite. There may be considerable proliferation of the capsular cells of the glomeruli, presumably a reaction to the excreted myoglobin or its breakdown products. The first convoluted tubules appear normal, but, from the loop of Henle downwards, degenerating and regenerating epithelial cells crowd into the lumen, while some of the collecting tubules and excretory ducts are filled with a mass of proliferating cells. The interstitial tissue of the boundary zone and medulla is still oedematous and infiltrated with plasma cells, lymphocytes, and histiocytes, but now begins to appear more fibrous.

Other Areas

Liver.—There are no specific changes, but there is usually a centrilobular degeneration with a round- or mixed-cell infiltration of the portal areas.

Lungs.—Patchy oedema, small areas of collapse with compensatory emphysema, and early inflammatory changes in some bronchi were evident, but in no case did it appear likely that the lesions would play an important part in the clinical picture.

Cardiac and Smooth Muscle.—Apart from mild incidental fibrosis in two cases, no lesions have been found.

Other Organs.—The thyroid gland in Case 2 showed deficient colloid and many of the cells were necrotic, but the gland was normal in Cases 4 and 5. No significant lesions were seen in other organs. Professor William Blackwood has kindly confirmed the absence of histological changes in the nervous system.

Discussion

The pathology of sea-snake poisoning in man differs significantly from that reported in animal experiments. In human victims the primary histological lesion is necrosis of skeletal muscle. The myonecrosis occurs rapidly and is clinically apparent and widespread within half to one hour of the bite. Table II shows the extent and severity of the necrosis 14½ hours after the bite. These lesions are obviously sufficient to explain the chief symptom of sea-snake toxaemia—muscle movement pains and stiffness—as well as the paresis which ensues later. Since generalized muscle movement pains develop so soon after the bite, it is probable that sea-snake venom attacks the cell membrane of skeletal muscle directly in human victims. Myoglobinuria is proof of myonecrosis, although it does not indicate the cause. Professor J. H. Dible kindly examined sections of muscle from Case 3 and kidney from Case 7 and confirmed that the histological changes in both were indistinguishable from those he had found in experimental clostridial poisoning and in idiopathic myoglobinuria. Why does part of the muscle so often escape visible damage in such cases? Also, why is smooth and cardiac muscle so resistant? In no case were histological lesions attributable to the toxaemia found in smooth muscle or the myocardium.

Distal tubular necrosis was present in kidneys of all victims surviving longer than 48 hours. In these cases acute renal failure appeared to be the immediate factor

causing death. Experimentally, Bywaters and Stead (1944) showed that myoglobin injected into healthy rabbits caused no renal damage unless the urine was acidified. It is therefore unlikely that the myoglobin released in sea-snake poisoning is solely responsible for the renal lesions. Is the venom nephrotoxic? Reid and Jenkins (1948) showed that cobra venom acted directly on the kidney of eviscerated adrenalectomized cats, causing liberation of rennin. Hypertension was observed in Case 1 and 3; progressive hyperkalaemia was the immediate cause of death in Cases 1 and 5. Renal damage may be mainly responsible for these two features—a renal pressor factor leading to hypertension while progressive hyperkalaemia arose because diminished renal excretion failed to cope with the extra load from cellular release of potassium. Against this concept of sea-snake venom being directly nephrotoxic is the paucity of visible damage in patients dying within 24 hours of the bite. By analogy with the skeletal-muscle lesions so evident in sea-snake poisoning one would certainly expect to find renal necrosis even when death occurs shortly after the bite. We have been unable to demonstrate the fine fatty globules which Graber and Sevitt (1959) found in the glomerular tufts and which they thought might be a histological sign of structural changes affecting glomerular filtration in burned patients.

The liver may appear distinctly pale at necropsy. Feldberg and Kellaway (1938a) described depigmentation and release of adenyl compounds from the liver experimentally perfused with cobra venom. Similar depigmentation occurred with staphylococcal toxin, mercuric chloride (Feldberg and Kellaway, 1938b), and clostridial toxin (Kellaway, Reid, and Trethewie, 1941). The centrilobular degeneration in sea-snake poisoning may therefore be due to direct venom damage. In Case 2 there was no obvious clinical explanation why death occurred when it did (Reid, 1961): in such cases liver damage may be an important factor.

Clearly, there are important differences in pathology between sea-snake poisoning in man and in the animals so far reported. Myonecrosis was not found at necropsy on a goat which died 30 hours after injection of *E. schistosa* venom; rabbits dying acute deaths showed no lesion in muscle, liver, or kidney (Carey and Wright, 1960). Possible explanations for these discrepancies include: (1) species may differ in their reactions; (2) some change occurs in sea-snake venom during desiccation; and (3) myonecrosis has been overlooked. To elucidate the problem we have recently injected dogs with *E. schistosa* venom, both freshly obtained and reconstituted from dried venom. In each case typical widespread necrosis of skeletal muscle was histologically evident. This suggests that myonecrosis has previously been overlooked.

Summary

The principal pathological lesion of sea-snake poisoning in man is necrosis of skeletal muscle.

As with other types of myonecrosis, renal damage often results.

Histological changes in the nervous system and in smooth and cardiac muscle are notably absent.

We thank Professor William Blackwood and Professor J. H. Dible for their help and interest.

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HYPOVITAMINOSIS-A IN A FAMILY WITH TYLOSIS AND CLINODACTYLY

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Tylosis palmaris et plantaris constitutes one of the group of polykeratoses (Touraine, 1954) and is a rare familial ectodermal anomaly of the palms and soles characterized by marked hyperkeratosis. The most comprehensive review of the subject is that of Cockayne (1933).

The association between various hyperkeratotic and dyskeratotic skin diseases and hypovitaminosis-A has been noted (Rapaport *et al.*, 1942; Peck *et al.*, 1943a, 1943b; Leitner and Moore, 1946; Leitner and Ford, 1947). Low blood levels of vitamin A were found in tylosis (Porter, 1951) and some improvement in the skin lesions occurred on giving high doses of the vitamin.

The present report is a study of a tylostic patient who was admitted to hospital with a myocardial infarction and a good description of tylosis in the family. The histopathological and clinical features of tylosis in this family have been more extensively dealt with in an earlier publication (Klintworth and Anderson, 1961).

Materials and Methods

A family of 59 members through five generations was investigated. Wherever possible they were personally interviewed. Where this was not practicable a first-hand collaborative description was taken from several other members of the family. Particular attention was paid to the presence of tylosis, cardiovascular disorders, manifestations of hypovitaminosis-A, and dysphagia. In those deceased the cause of death was ascertained. Specimens of blood were taken from willing members for estimation of the serum vitamin A, carotene, and lipid.

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The levels of serum vitamin A and carotene were estimated by the method of Pett and LePage (1940). Lipoprotein partitions were carried out on fasting specimens of blood. A dietary history was obtained, and special attention was paid to the carotene and vitamin-A content of the diet.

The propositus was in addition tested for dark-adapted visual acuity, using a Feldman adaptometer; his protein-bound iodine and vitamin-A uptake were determined; skin was biopsied for histology and vitamin-A autofluoroscopy.

Results

The family tree is illustrated in Fig. 1. There were at least 14 members with tylosis (9 female, 5 male). Of the 32 members personally examined 11 were affected; a good description was obtained regarding three others. The extent and severity of the skin lesions were largely determined by occupational and climatic factors. Thus there was an aggravation of the skin condition during cold dry weather or, in the case of the hands, after prolonged manual labour. In addition, 10 members (6 female, 4 male) had clinodactyly—a curving-in of the little finger. This was associated with tylosis in six of the 10 cases.

Two other members besides the propositus had sustained a myocardial infarction. Of the seven known deaths, three were due to "heart disease" and none to malignancy. None of the family complained of night blindness, but this was not unexpected, as all were city dwellers.

Vitamin A.—The results of the biochemical findings are given in Table I. The fasting values of vitamin A were subnormal in the eight cases with tylosis, while the carotene levels were within normal limits. Two members (III 17 and III 14), although in the direct line of descent, did not have tylosis, but were hypovitaminotic-A. The propositus and his affected child did not benefit from vitamin-A therapy in high doses.

Lipoprotein Partition.—The results are shown in Table II. Several members exhibit evidence of hyperlipaemia, hypercholesterolaemia, and raised beta-lipoprotein fractions. There is, however, no constant association with either clinodactyly or tylosis.

The protein-bound iodine in the blood of the propositus was normal and his dark-adapted visual acuity was at the lower limit of normal. Autofluorescence of the skin showed the presence of carotene in the epithelium, especially in the stratum corneum. Vitamin A was absent in the skin.

Histologically the skin showed considerable hypertrophy of all its layers, more especially of the stratum corneum, which was greatly thickened. The stratum granulosum was normal in appearance and there was no change in the stratum spinosum. The papillae were increased in depth. The dermis was unaffected.

TABLE I.—*Vitamin A and Carotene Levels*

Family Member	Vitamin A I.U./100 ml.	Carotene mmg./100 ml.	Family Member	Vitamin A I.U./100 ml.	Carotene mmg./100 ml.
Average normal	70	60–300	III 12	3	112
			III 13	43	138
			III 14	32	65
II 2	15	72	III 17	0	123
II 5	6	102	IV 17	0	146
III 4	79	65	IV 18	21	82
III 8	22	72	IV 19	0	150

TABLE II.—*Lipoprotein Partition*

Family Member	Total Lipid mg./100 ml.	Total Cholesterol mg./100 ml.	Cholesterol		Cholesterol %		Lipoprotein %	
			Free mg./100 ml.	Esters of mg./100 ml.	$\alpha_1\alpha_2$ Lipoprotein	β Lipoprotein	$\alpha_1\alpha_2$ Lipoprotein	β Lipoprotein
Adult average normal	400–600	160–250	45–65	115–185	15–33	67–85	25–50	50–75
II 2	813	172	52	120	19	81	21	79
II 5	956	372	114	258	19	81	26	74
III 4	1,109	263	78	185	24·5	75·5	—	—
III 8	1,287	331	97	234	12·5	87·5	18·5	81·5
III 12	1,415	392	104	288	10	90	7	93
III 13	1,207	242	68	174	15	85	11	89
III 14	567	172	46	126	26	74	34	66
III 17	891	272	69	203	18	82	17	83
IV 17	665	228	58	170	22·5	77·5	26·5	73·5
IV 18	701	232	55	177	19	81	32	68
IV 19	591	209	—	—	—	—	—	—

Discussion

Vitamin A and Carotenoids

Vitamin A has an inhibiting effect on keratinization in epithelial cells. Defective metabolism of vitamin A, or hypovitaminosis-A, seems to be causally related to hyperkeratosis and other disorderly behaviour of

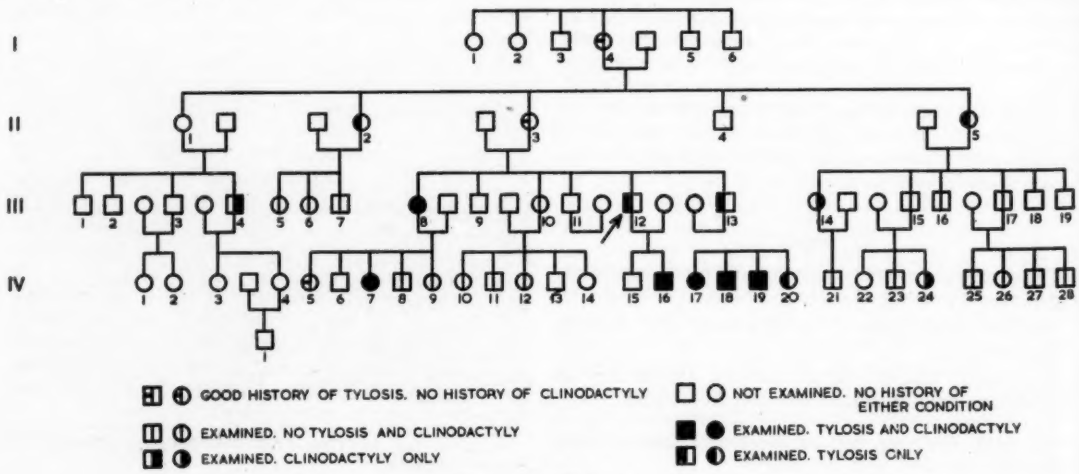

FIG. 1.—Family tree

epithelial tissues. Despite its importance to the skin, vitamin A is not present in the normal epidermis (Popper, 1941, 1944; Cornbleet and Popper, 1942), and this finding was confirmed in the hyperkeratotic skin of our case. Porter (1951) found the serum-vitamin-A levels to be low in the six cases of tylosis which he studied, while the carotenoids were normal. This is in accord with our findings. Hypovitaminosis-A has been described in Darier's disease (Peck *et al.*, 1943b), and several authors have used massive doses of vitamin A in their cases. Although there was some improvement the skin did not become quite normal, suggesting that there may be other factors besides the impaired vitamin-A metabolism involved in the aetiology of Darier's disease (Barwasser, 1941; Michelson, 1942; Abramovitz, 1942; Peck *et al.*, 1943b).

Low levels of serum vitamin A have also been noted in ichthyosis (Rapaport *et al.*, 1942; Peck *et al.*, 1943a; Leitner and Moore, 1946), pityriasis rubra pilaris (Leitner and Moore, 1946; Leitner and Ford, 1947)—the similarity of the latter to the lesions found in vitamin-A deficiency has been stressed by Pettler (1936) and by Sutton and Sutton (1949)—and less frequently in commoner skin diseases such as eczema and psoriasis (Marchionini and Patel, 1937). Moore (1957) differentiates between skin lesions due to "dietary" and those due to "secondary" vitamin-A deficiency. Representatives of the latter are the conditions noted above. The dietary type—phrynoderma of Nicholls (1933)—takes the form of hyperkeratosis of the hair follicles, which becomc hard and protuberant. Such follicular hyperkeratosis due to vitamin-A deficiency is rare in Britain (Bicknell and Prescott, 1953), but is not uncommon in the African (Loewenthal, 1933).

The reason for the low levels of serum vitamin A in tylosis is not known. A deficient intake has been postulated, but the members of the family studied by us were all on a normal adequate diet. In areas in the Far East where the diet is low in vitamin A, tylosis is not more frequent than in any other part of the world (Dencer, 1953).

In regard to poor absorption, no members took liquid paraffin, which hinders uptake of vitamin A, and the vitamin-A-absorption test carried out on the propositus after fasting was normal, suggesting that intestinal absorption was adequate. However, defective absorption has been described in various skin lesions (Ruch *et al.*, 1946).

Carotene estimation alone is of value only in showing that carotene absorption is unimpaired. When vitamin A is estimated at the same time, an indication of the efficiency of conversion of carotene to vitamin A is gained (Bicknell and Prescott, 1953). In our study normal carotene with low levels of serum vitamin A was present, and poor conversion of provitamin to the vitamin should be considered.

Reduced storage capacity of the liver has been cited as a possible mechanism. In view of the incidence of heart disease and hyperlipaemic tendency in our family, it is interesting to note Moore's (1957) finding that the livers of people dying of coronary artery disease contain 100 I.U./g. of vitamin A as opposed to the approximate normal average of 200 I.U./g.

Increased utilization of vitamin A was excluded, as no member had any disease in which hypovitaminosis-A is known to occur as a complication, such as febrile conditions (Moore, 1957). However, the possibility of increased katabolism of vitamin A by the hyperkeratotic skin should be borne in mind.

The association between tylosis and low serum vitamin A may be purely coincidental, but, since we are dealing with a primary genetic condition, an explanation in this field may be sought, as suggested by Jeghers 1943).

It is possible that there is a genetic disturbance involving a single gene which has led to a metabolic defect producing on the one hand tylosis and on the other low serum vitamin A. Such a mechanism would illustrate the pleiotrophic effect of a single gene. Two genes situated on one chromosome—that is, linked genes—may be involved, the one resulting in tylosis, the other in low serum vitamin A. Another possibility is that of a single gene leading to a metabolic disturbance which results in a low serum vitamin A—the latter ultimately manifesting as tylosis. However, no clear relationship exists between the vitamin-A level and the severity of the disease, and this was shown in our cases. Moreover, work in the experimental field does not support the idea of a primary causal relationship (Moore *et al.*, 1935; Hale, 1937; Davis and Madsen, 1941), and the skin lesions of dietary vitamin-A deficiency are quite distinct from tylosis.

Finally, the theoretical possibility of a gene resulting in some metabolic disturbance with production of tylosis must be considered. In this case there may be a disturbance in the function of the epithelial cells with consequent defective metabolism of vitamin A. The low levels of the latter therefore are the end-result of the skin disorder and not the primary cause. This would explain the finding that the level of vitamin A does not always correlate with either the severity or the extent of the skin lesion (as shown in our cases) and for the difficulty the epidermal cells seem to have in utilizing vitamin A normally (Fraser, 1949).

Blood Lipids

Blood cholesterol levels in patients recovering from various diseases were noted to increase after large doses of vitamin A (Lasch, 1934). Josephs (1944) observed a rise in lipids and cholesterol after vitamin-A administration and felt that vitamin A had an important and specific effect on the metabolism of lipoids. Recent workers could find no abnormality in the levels of cholesterol in the plasma or livers of rats deficient in vitamin A (Green *et al.*, 1955). In our family, however, several members with hyperlipaemia, hypercholesterolaemia, and elevated beta-lipoprotein fractions (to which carotene and vitamin A attach in the serum) had very low levels of vitamin A. In these instances the vitamin had not "drifted with the metabolic tide" (Moore, 1957). Sinclair (1953) felt that the possible deficiency of an essential fatty acid in tylosis should be considered. He has postulated a similar mechanism in the genesis of atherosclerosis (Sinclair, 1956).

Genetics

Tylosis is inherited as a Mendelian dominant with a high degree of penetrance. It appears to be controlled by a single autosomal gene. The sexes are equally affected and no race is immune (Cockayne, 1933; Sutton and Sutton, 1949; Scott, 1953). Lawler and Renwick (1957) believe that there are at least two types of inherited tylosis. These forms have been differentiated clinically, apparently run true to families, and

appear to be due to different genes. The lesions vary not only at different times in an affected individual but also in intensity and extent in members of the same family. Such differences are largely determined by genetic and environmental modifiers.

Tylosis and other ectodermal dysplasias have on rare occasions been found together with mucosal leucoplakia (Kumer and Loos, 1935; Touraine, 1954). The development of carcinoma in this premalignant lesion may be expected. Howel-Evans *et al.* (1958) noted a significant association between carcinoma of the oesophagus and tylosis in two families. There was no mention of leucoplakia in their cases. We found no evidence of leucoplakia or of oesophageal malignancy in our family. The possible relationship between ectodermal anomalies, various hyperkeratotic skin lesions, and low serum vitamin A has been alluded to by Porter (1951). Serum vitamin A was not estimated in the cases studied by Howel-Evans *et al.* (1958). It is well recognized that vitamin A is concerned with the integrity of epithelial structures and that in states of deficiency hyperkeratosis or squamous metaplasia may occur. Boyd (1947) has pointed out that squamous carcinoma may develop from squamous metaplasia. Regarding the participation of vitamin A in carcinogenesis there is no complete agreement.

Early workers in the experimental field (Fujimaki, 1926; Saiki and Fujimaki, 1927; Goldblatt and Benischek, 1927) indicated that while vitamin A did not appear to have a primary participation in carcinogenesis it was an important factor. However, other workers (de Ruyter, 1934; Fridericia *et al.*, 1940; Brunschwig and Rasmussen, 1941) could not substantiate this claim. On the basis of histological observations and a review of the literature, Popper and Ragins (1941) concluded that vitamin A had no bearing on the causation of tumour. The relationship between vitamin A and carcinoma has been extensively reviewed by Stern and Willheim (1943).

Clinodactyly was observed in our family (Fig. 1), and we can find no previous literature reporting the association of this condition with tylosis. Clinodactyly comprises a shortening of the middle phalanx of the fifth finger, mainly on its radial aspect, resulting in a radial deflection of over 15 degrees of the terminal phalanx (Figs. 2 and 3).

The term "clinodactyly" should be confined to those cases of crooked little finger due to incomplete ossification. There is no flexion deformity and the rest of the digits are normal (Hersh *et al.*, 1953). Transmission is via an autosomal dominant. Incomplete penetrance was noted in that in at least eight cases the parents did not have the anomaly. In one of these cases (IV 24) there was no clinodactyly in the parents or grandparents.

The presence in a family of two genetically determined abnormalities is an uncommon finding (Roberts, 1959). Accepting Swan's (1956) incidence for tylosis as 1 in 40,000 and that of the more common clinodactyly as 1 in 1,000 (Hersh *et al.*, 1953), it will be realized that the probability of these two conditions occurring together by chance is of the order of 1 in 40 million.

The coexistence of two genetically determined entities may be due to genetic linkage of the two abnormal genes. Genes are called linked when they are situated at loci on the same chromosome pair. The problem of linkage studies in man is complicated by the extreme difficulty of obtaining pedigrees of a sufficient magnitude to be statistically significant. Another hazard is the phenomenon known as "crossing over," which may allow dissociation of the genes if they are not closely situated on the chromosomes. Methods of determining genetic linkage by comparison of siblings with one another were developed by Penrose (1935, 1938). These techniques are based on the fact that if the siblings receive the same chromosome from a parent there will be an increased probability that the siblings will be phenotypically alike. Furthermore, they will more probably be alike in any trait determined or influenced by a gene located on that chromosome. Ultimately a correlation is established between sibling likeness in one trait and sibling likeness in the second trait, genetically linked to the first. By means of such methods in the present family we were unable to obtain results which were statistically significant for linkage. These results, however, do not exclude the likelihood of the two mutant genes being situated on the same chromosome. The possibility of tylosis and clinodactyly being due to the pleiotropic effects of a single gene seems unlikely, as this association of the two conditions has not been previously reported. Finally, their association may be the result of genes situated on different chromosomes.

FIG. 2.—Photograph showing clinodactyly.

FIG. 3.—Radiograph of right hand showing clinodactyly.

Summary

A family exhibiting tylosis plantaris et palmaris and clinodactyly was investigated. At least 14 of the 59 members had tylosis and 10 had clinodactyly. Six cases had both conditions.

In eight of the members with tylosis the values of serum vitamin A and carotene were estimated. In all

cases the serum vitamin A was subnormal while that of carotene was within normal limits. The role of vitamin A in tylosis and various other skin conditions and its possible relationship to squamous metaplasia and carcinoma are discussed. The metabolism of vitamin A and its functions in maintaining the integrity of epithelial structures is still poorly understood. Some of the possible genetic mechanisms underlying this association between low serum vitamin A and familial skin diseases are outlined.

In addition to the propositus, two other living members had sustained a myocardial infarction. Hypercholesterolaemia and hyperlipaemia were noted in several members, but were unrelated to tylosis, clinodactyly, or serum vitamin A.

Tylosis is transmitted via a monomeric autosomal dominant gene with a high degree of penetrance. The expressivity of the condition is governed to a large extent by environmental modifiers. Clinodactyly is inherited as a non-sex-linked Mendelian dominant with low penetrance. The explanation for the coexistence of two genetically determined entities is considered, and in the case of tylosis and clinodactyly we feel that the association is due either to distant linkage or to the genes being on different chromosome pairs.

We are grateful to Professor G. A. Elliot, Professor B. J. P. Becker, and Professor P. V. Tobias for advice and constructive criticism; to Dr. W. M. Politzer (South African Institute for Medical Research), who carried out the biochemical estimations; to the photographic unit of the Department of Medicine, University of the Witwatersrand, for Fig. 1. All three illustrations are reproduced here by kind permission of the Editor of the *South African Medical Journal*.

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HEREDITARY BRANCHIAL DEFECTS IN A HAMPSHIRE FAMILY

BY

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This paper records the occurrence of multiple congenital branchial defects in several members of a family covering four generations. A number of similar inherited anomalies have been described previously, but in this particular group multiple lateral cervical sinuses were associated with maxillary malformations and ear-pits, a combination which does not appear to have been reported before.

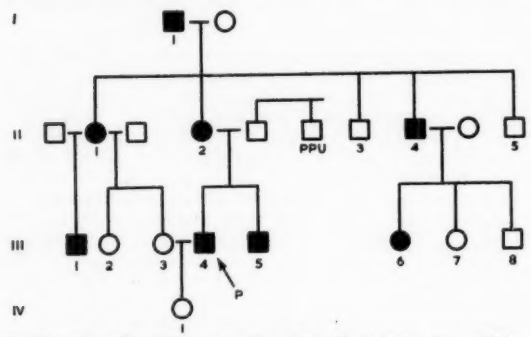
The grandfather of the propositus was a Wiltshire man. His daughter married a Hampshire farm labourer, moved to a small village near Winchester, and with her increasing progeny has remained in this area ever since. The family group comprised 21 members; 15 were blood relatives, and eight of these possessed abnormalities. The affected persons were the grandfather himself, two of his daughters and one of his sons, and three grandsons and one granddaughter. I examined four normal and three affected relatives. The remaining 14 members, including five affected persons, were either dead or untraceable at the time of inquiry. The descriptions of these are thus unfortunately only second-hand, being provided from the memories of the relatives personally examined; but, since these tallied though supplied without prior collusion, they are probably reliable. These people were uncertain about the presence of ear-pits in the other affected relations, but this is not surprising, as these small malformations are quite unobtrusive.

The ear-pits when present were situated in the upper anterior end of the helix, being about 1 mm. wide and 1 mm. deep. They were observed only in the propositus and his brother. There were two maxillary abnormalities, always coexistent. The upper front teeth projected forward at an angle of some 20 to 30 degrees from the vertical, giving a slightly simian cast to the facies. The hard palate was high and arched, equally on both sides. The lateral cervical sinuses were typical of their kind. Their openings in the skin were 2 to 3 mm. in diameter and were always located in the anterior line of either sternomastoid muscle at various levels. Their depth was not probed. They usually caused little trouble, but when a collar was worn were inconvenient

because of their tendency to exude small quantities of clear fluid. The brother of the propositus was the only person in the group to be ever more than merely irritated by his defects. His lower left sinus had become infected several times, with on one occasion a cellulitis which spread down over the chest and brought him near to death. The sinuses were bilateral in every case, though often at different levels on each side, and in some they were multiple.

The three affected members personally examined were the propositus, his brother (III 5), and his mother (II 2). The propositus had the maxillary malformations, a left ear-pit, and a pair of lateral cervical sinuses. The right-sided sinus lay at the level of the inferior margin of the thyroid cartilage, while that on the left was situated a little higher, nearly lateral to the junction of the superior horn with the main thyroid cartilage. The brother, III 5, had a similar ear-pit and maxillary anomalies. He had besides, however, no fewer than four of these sinuses. Two were at the same level—one about 1 in. (2.5 cm.) above the anterior clavicular insertion of each sternomastoid muscle; another was just below and behind the left mandibular angle; and a fourth was a little inferior and anterior to the lobe of the right ear. The mother, II 2, had no ear-pit, but the maxillary defects were well developed. Her two sinuses were situated at the same level, one immediately in front of the clavicular insertion of each sternomastoid. The father, paternal uncle, wife, and daughter of the propositus were personally examined and found to be normal in all respects.

The five affected members not examined were I 1 and II 1, who were both dead; and II 4, III 1 and 6, whose whereabouts were unknown. They all were said to have had at least two similar sinuses in their necks, high palates, and upper front teeth which "stuck out." Two maternal uncles, II 3 and 5, and three cousins, III 2, 7, and 8, were not examined, but were said to be unaffected. Three spouses not examined—the two husbands of II 1 and the wife of II 4—were also said to be normal, and, so far as these people knew, were at least not closely related. Neither the father nor the paternal uncle of the propositus knew of any relationship between themselves and these other spouses, or between the spouses individually "as far back as they could remember."



Family tree. ■=Affected male. ●=Affected female. PPU=Paternal uncle of propositus.

Discussion

Neither congenital lateral cervical sinuses nor ear-pits are uncommon isolated anomalies. Ewing (1946) observed ear-pits in 0.9% of 3,500 British Service men, and Stannus (1914) found them in 4.5% of 6,491 Bantus in Nyasaland. But they are unobtrusive, usually trouble-free, and thus may pass unnoticed for years by their owner even if he is medically qualified (Fourman and Fourman, 1955).

Aird (1958) states that careful search will reveal a family history of fistula or accessory auricle in some 25% of cases of lateral cervical ("branchial") fistula. Previous reports of the occurrence of such malformations in several members of a family include those by Paget (1877), Kindred (1921), Přecechtěl (1927), Whitney (1939), Edmonds and Keeler (1940), Quelprud (1940), Kinder (1954), Fourman and Fourman (1955), and Wilson (1955). None of these mentioned an associated high arched palate as appears in this family. The only instance of dominant inheritance of such a defect given by Gates (1946) is that integral in the well-known condition of arachnodactyly, but none of the members of the above family showed any other stigmata of that syndrome.

When ear-pits occur alone or with lateral cervical sinuses as the only other associated anomaly, the apparently dominant inheritance shows incomplete or irregular penetration (Kindred, 1921; Edmonds and Keeler, 1940; Royk-Lewinski, cited by Quelprud, 1940), sometimes "skipping" of generations (Whitney, 1939), or may appear in only one of uniovular twins (Quelprud, 1940). However, when a further concurrent abnormality is present, such as deafness (Přecechtěl, 1927; Fourman and Fourman, 1955), or a high palate as in this family, the dominance seems to be enhanced, so that the penetrance of the combination as an entity becomes more complete. This family report further confirms the evidence of previous accounts in demonstrating that either sex may manifest and transmit hereditary branchial developmental abnormalities.

For what such small numbers are worth in deducing gene characteristics, the proportion of 8 to 15 presenting here suggests a simple dominant mode of inheritance, and the pattern of appearance of the defects throughout the pedigree strongly supports this form of transmission. Interest focuses naturally upon the consanguineous marriage between the propositus and his cousin. Although this woman came from an affected mother, II 1, neither she, III 3, nor her daughter, IV 1, by the propositus showed any of these defects. This normalcy of the wife and daughter of the propositus admittedly could mean that the woman II 1 was homozygous recessive and, with her second husband either normal or a heterozygous recessive carrier, that III 3 and her daughter were therefore heterozygous carriers. But were this gene or character complex recessive, the pattern of transmission from the other matings could be explained only by heterozygous possession of an identical recessive factor by no fewer than four different unrelated spouses—the wife of I 1, the husband of II 1, the husband of II 2, and the wife of II 4. This is unlikely, whereas simple dominance explains every manifestation of this defect pattern.

It would appear, then, that the linkage between the character for lateral cervical sinuses and that for ear-pits is ordinarily weak; so that the pair may separate during nuclear division, cross over, and "recess" among normal genes. In this reported family it seems that the advent of yet another abnormal character, for maxillary defect, has consolidated the linkage between all three to produce a complex which, when transmitted, behaves as a full dominant.

Summary

A family of fifteen persons is described wherein eight members in three generations exhibited closely linked congenital anomalies comprising multiple branchial malformations and maxillary defects. The complex is

revealed to have been inherited as a simple dominant, uninfluenced by sex in either transmission or penetration. The literature is reviewed and the heredity discussed.

I am indebted to Dr. W. D. Brinton, of the Royal Hampshire County Hospital, and Dr. F. G. Lougee, of Micheldever, for access to their patients. I am grateful to my colleagues in the Winchester Area Pathological and Public Health Laboratories for their comments and helpful criticism in the preparation of this paper.

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Medical Memoranda

A Case of Artificial Abdominal Urethra

Early in 1959 I was fortunate enough to see a demonstration by Lapides at Michigan University Hospital, Ann Arbor, of a boy who, as a result of a fracture of the pelvis, developed a urethral stricture, and in whom the urethral canal could not be reopened. The child was passing his urine through an abdominal urethra, was perfectly continent, and had complete control over urination.

Back in Mauritius, I was confronted with a similar case.

CASE REPORT

An Indian schoolboy, aged 11 years, was admitted into hospital on July 16, 1958, suffering from a fracture of both rami of the right os pubis and passing blood per urethram, as the result of a street accident. The surgeon who attended him found a complete rupture of the urethra, with extravasation of blood into the cave of Retzius and paravesical spaces. Subsequently several attempts at external urethrotomy failed for various reasons, and when I saw the boy in April, 1959, he had a de Pezzer catheter draining the bladder through a suprapubic cystostomy wound.

Bougienage and urethroplasty having failed, an attempt was made on April 8, 1960, to fashion an artificial abdominal urethra, as described by Lapides.

Under a general anaesthetic, a median incision extending from the umbilicus to the symphysis pubis was made and the peritoneal cavity opened. The bladder was detached from the abdominal wall and the cystostomy wound closed with No. 2 chromic catgut. An area of the anterior bladder wall, measuring four centimetres square, was mapped out. Three sides of the square were cut out to form a flap of bladder wall with the base attached to the dome of the viscus. The flap was converted into a tube, the sides being stitched in two layers with No. 2 chromic catgut, the first layer to approximate the sides and the second layer to invaginate. The defect in the bladder was similarly closed by two layers of chromic No. 2 catgut. The open end of the tube was passed through the linea alba and skin, away from the abdominal recti. The mucosa of the mouth of the bladder tube was stitched to the skin. The abdominal wound was closed in layers and the bladder was drained by a rubber catheter passed through the artificial urethra thus formed. The patient was placed on antibiotics.

After 14 days the catheter was removed. It was then found that the boy could hold his water for half an hour, and when he micturated there was a small stream and a lot of dribbling down his abdominal wall. Within a week he was able to hold his water for a period of two hours and could get a good jet, as shown by the accompanying photograph.

When he was discharged from the hospital on June 1 he was perfectly continent. When seen six months after the operation he was found to be completely continent, and got up only once a night to empty his bladder.

In Lapides's cases there was no residual urine, but in the present one there was a residual urine of about 5 ml. Cystography after micturition showed a small pool at the natural neck of the bladder. It is doubtful if this residue, situated right at the bottom of the bladder, can ever be got rid of.

My thanks are due to Dr. E. Losonczi, Director of Medical Services, Mauritius, for his permission to publish this report.

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REFERENCE

Lapides, J. (1958). *J. Urol.*, **80**, 341.

The MINISTER OF LABOUR, Mr. John Hare, has used his powers under the Factories Act, 1959, to reappoint the Joint Standing Committee on Health, Safety and Welfare in the Drop Forging Industry. The function of the committee, which has been appointed for three years, is to advise the Minister on matters affecting the health, safety, and welfare of persons employed in the drop forging industry.

Reviews

EXPERIMENTS IN PERSONALITY

Experiments in Personality. Volume 1: Psychogenetics and Psychopharmacology. Volume 2: Psychodynamics and Psychodiagnostics. Edited by H. J. Eysenck, Ph.D. (Pp. 262 +xxii, illustrated; and pp. 333+viii, illustrated. 40s. each.) London: Routledge and Kegan Paul. 1960.

These two volumes contain further contributions to the impressive volume of work carried out by Professor Eysenck and his team in the department of psychology at the Institutes of Psychiatry, London University, over the past 15 years. These inquiries have sought to define the main dimensions of normal and abnormal personality by the application of factorial analysis to the results of personality tests. Three main factors emerged from these inquiries—a general factor of "neuroticism," a bipolar factor closely related to Jung's introversion-extraversion dichotomy, and a factor of "psychoticism." After these preliminary statistical and taxonomic studies, Professor Eysenck moved forward to experimental inquiries into the psychophysiological basis of the dimensions he had isolated. Integrating his findings with the theories of Pavlov and Hull in relation to conditioning and learning, he proposed that introversion-extraversion was closely related to differences in conditionability between individuals; the introvert formed conditioned responses that were strong, that developed with speed, and that were resistant to extinction, while the responses of extraverts showed the converse of these features. Similar variations in the responsiveness of the autonomic system were held to be related to "neuroticism." Eysenck further predicted that depressant drugs by their increase of cortical inhibition and decrease of cortical excitation would tend to produce extraverted behaviour patterns, while stimulant drugs would exert an opposite effect.

The testing of these deductions has led to experimental work in relation to perception and learning and the effects of brain injury and drugs on psychological performance. In these volumes this work is carried a stage further with inquiries into the relationship between measures of learning, attention, and conditioning and introversion-extraversion and effects of depressant drugs upon perceptual discrimination, vigilance, reaction time, and palmar skin resistance. In an inquiry into thought disorder in psychotic patients, schizophrenics (as distinct from neurotics, depressives, and normals) were found to be over-inclusive in their thought, but no more "concrete" in thinking than other subjects with similar intelligence, nor any less retarded than depressives.

There is a group of papers on canonical variate analysis, a statistical technique based upon different assumptions than factorial analysis, but which leads to essentially similar conclusions about personality structure. Ingenious use of it is made by the Eysencks for the development of a method of classification of drugs in terms of their effects on performance in psychological tests. Some of the findings in the experimental inquiries confirmed the predictions made. Thus, hysterics and dysthymics behaved in most tests of attention, learning, and perceptual tasks "in a manner suggestive of, respectively, high and low levels of central inhibition." One depressant drug decreased the number of conditioned responses but another failed to produce a significant effect. A number of the findings, moreover, failed to substantiate the initial postulates. Thus, the conditioning measures employed by Willett did not, on the whole, correlate with extraversion–introversion, nor was there the predicted correlation between perceptual tests and extraversion that might have suggested they were different aspects of the same process.

Professor Eysenck's confidence in his theories seems unshaken by such discrepancies. He regards his theories as belonging to the "weak" category for which successful predictions provide support, whereas failures, which would have been disastrous for a "strong" theory, need not be taken too seriously. It is often wise as well as courageous, when working in a relatively unexplored field, not to allow a single "brute fact" to destroy a beautiful hypothesis. But it then needs a rare objectivity and discernment to avoid the danger of propping up a tottering theory with the aid of *ad hoc* explanations.

In some respects Dr. Eysenck's views are not essentially different from those of the psychoanalysts he has criticized so vigorously and often. Thus, he holds that neuroses are neither innate nor due to subtle lesions, but the product of past experience. His view that both normal and abnormal behaviour may be described in terms of the same dimensions of personality would have been approved by Freud. Although such emphases have had the valuable effect of broadening the perspectives of clinical work and scientific inquiry in relation to mental disease, they are none the less one-sided, for they ignore the sharp discontinuities between health and disease, strongly suggesting the entry of new elements in neurotic as well as in psychotic disorders. It is these that constitute the psychiatrist's specific problem and are for him the focus of interest. The psychiatrist will look in vain in the description of the case material in these volumes for the operational definitions that governed the selection of patients or for information on whether they were in the early or late stages of an attack, in remission or relapse, subject to illnesses of long or short duration.

Although Dr. Eysenck was right to push his particular approach as far as it would go in the field of abnormal psychology, his theories are without compelling quality or capable of affording to the psychiatrist, at any rate, the intellectual and aesthetic satisfactions so characteristic of fruitful new theories, even in their "weak" stage. One suspects, therefore, that it may ironically prove that Dr. Eysenck's studies have, like Freud's investigations, taught us more about those characteristics of psychiatric patients which they share with normal subjects than those in respect of which they differ from them. But his contributions, and those of his group, to the objective, scientific investigation of human behaviour are remarkable in their range and comprehensiveness and will probably prove lasting.

MARTIN ROTH.

DELAY IN CANCER

Cancer. The Significance of Delay. By Robert Sutherland, M.D., D.P.H. (Pp. 206+ix+7. 30s.) London: Butterworth and Co. (Publishers) Ltd. 1960.

Everyone knows that many patients when suffering from symptoms of cancer delay seeking medical advice, and no one would deny that if this delay were reduced and patients came more promptly the results of surgical treatment would be better. The real question is, how much is lost by this delay, or, in other words, how much would be gained by prompter treatment? This is not an easy question to answer, as Dr. Robert Sutherland

found when he began to investigate the significance of delay; but he has certainly made a profound study of the subject and written a most instructive and helpful book.

The problem is a difficult one because of the number of variable factors—the site of the tumour, the organs affected, the characteristics of the tumour and of the host and of the environment. Dr. Sutherland has not evaded these difficulties: he has faced them squarely one by one. And at the end of each chapter is a long summary and an even longer list of references. The book itself might be summarized by the last sentence but one in the last chapter, which reads as follows: "Although our knowledge of the causes of delay is far from complete, we know enough to at least reduce delay and thus to save or prolong lives that at present are unnecessarily or prematurely lost. We shall be culpably negligent if we fail to act."

CUTHBERT DUKES.

SHEFFIELD CORTICOTROPHIN CONFERENCE

ACTH. Proceedings of the Sheffield Corticotropin Conference held at Crewe Hall, University of Sheffield, January 7 and 8, 1960. Editor: Dr. H. F. West. (Pp. 135; illustrated. No price.) Malmo: Ferring Ab. 1960.

This is a verbatim account of a two-day conference on A.C.T.H. held in January, 1960, and attended by thirty-one laboratory and clinical workers, all of whom, with one exception, work in Great Britain. Topics discussed range from the chemical nature and bioassay of corticotrophins to the histological and enzymatic changes induced in the adrenal cortex and the diagnostic and therapeutic uses of the hormone. Perhaps too much was attempted in too short a time, because in some instances justice was not done to topics about which more is known, and in others too much time was devoted to speculative aspects needing more thoughtful study. None the less, this is interesting reading for physicians and research workers concerned with A.C.T.H., and, quite properly, it poses more problems than it answers.

R. I. S. BAYLISS.

DISEASES IN AFRICA

Non-infective Disease in Africa. The Peculiarities of Medical non-infective Diseases in the Indigenous Inhabitants of Africa South of the Sahara. By H. C. Trowell, O.B.E., M.D. (London), F.R.C.P. (Pp. 481+vii; illustrated. 70s.) London: Edward Arnold (Publishers) Ltd. 1960.

Dr. Trowell's name is well known in the literature on tropical medicine, to which he has made contributions of originality and distinction. He adds to these achievements the present book, which in effect collates the work of some thirty years spent in close observation of African patients in their native habitats combined with an extensive study of the work of others similarly engaged. The title may mislead; the book essentially is concerned with diseases seen in the African and not those to which the immigrant to Africa is subject. The volume is divided into chapters in each of which is described the disorders of an organ or a system. It begins with the liver, both normal and disordered; subsequent chapters are similarly concerned with the cardiovascular, the urinary, the alimentary, and other systems; the last chapter contains a brief but valuable discussion on the factors which influence the incidence of disorders and of diseases, and the forms they assume, among Africans.

To the doctor trained in Great Britain and destined to work in Africa the information available in this book will prove most helpful. He will find in it that results obtained by the standard laboratory and biochemical tests which are accepted as normal in Britain do not necessarily apply to the African population; that disorders commonplace in this country, such as coronary disease, are infrequent in Africans; that the converse—for instance, primary cancer of the liver—equally obtains; and that appendicitis is very rare in the unsophisticated African but more common in those adopting a European diet. Disorders due to inheritance and those following malnutrition feature largely in practice among Africans. These and innumerable other pieces of information obviously are of very great importance in the diagnosis of disorder in the sick African. This volume is a most useful source of reference for those carrying such a responsibility; it can unhesitatingly be commended as a very necessary addition to their equipment for service in Africa, and indeed elsewhere in the tropics.

A. R. D. ADAMS.

SPINAL FLUID

Cerebrospinal Fluid Dynamics in Health and Disease. By David Bowsher, M.A., M.D., B.Chir. (Pp. 80+xi; illustrated. 38s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961.

This book presents a brief but well-documented review of recent physiological studies and current views on the production and absorption of the spinal fluid and their application to the pathological problem of hydrocephalus. In this connexion the recent employment of radioactive isotopes has already made a significant contribution to our physiological understanding, but many difficulties and inconsistencies still stand in the way of a coherent hypothesis. Dr. Bowsher stresses that the spinal fluid is contained in a rigid system, rendered elastic only by the subarachnoid venous bed, which is responsible for the resting spinal fluid pressure; that water leaves and enters the spinal fluid with great rapidity across all its lining membranes; and that other substances enter it by diffusion through these membranes as well as by the active secretion of the choroid plexus. Hydrocephalus he regards as usually due to a vicious cycle in which rising pressure in the system progressively impairs leptomeningeal and vascular absorption.

The book can be read with profit by anyone interested in the clinical physiology of the spinal fluid. The reviewer must confess to some irritation caused by the frequent employment of the term "C.S.F." (which appears seven or eight times on many pages) instead of "spinal fluid."

HENRY MILLER.

HUMAN BLOOD GROUPS

An Introduction to Human Blood Groups. By Fulton Roberts, M.D. (Pp. 85+viii. 9s. 6d.) London: William Heinemann (Medical Books) Ltd. 1960.

Most recent books on blood groups stress their genetical aspect, since this is the one which has been the subject of the greatest advances in knowledge in the last twenty years. It is also one which bewilders many medical students, and indeed many qualified doctors. It is, however, the immunology of the blood groups which more directly gives them importance in medicine, and it is in dealing with this aspect that the present book is most effective.

The author adopts an unusual arrangement, introducing the principles of blood group serology and genetics by means of a detailed account of the Rh system, and combining with this a most readable account of the aetiology of haemolytic disease of the newborn. Only later, after dealing with several other systems, does he introduce the all-important ABO system. The book ends with clear summaries of the relation of the blood groups to disease, to genetics, and to anthropology, and finally a chapter on "some growing points," a very short select bibliography, and a good index.

While on the immunological side statements which might call for criticism are few, the author is not always so happy in his attempts to compress accounts of complex genetical situations, especially that involving the Rh factor, into small compass. For instance, the account of Fisher's theory of the Rh system, while essentially correct, would be difficult for a beginner to follow. At the beginning, Table III would prove confusing. It is indeed a tenable, if disputed, point that the sets of serological reactions shown in the vertical columns of this table are, as the author states, those of single "antigens", but what needs to be said about them at the outset is that the potentiality for making any given set is transmitted as a single genetical unit (explained by Fisher as due to a set of three closely linked genes).

The absence of detectable specific d (pp. 16 and 35) and O (p. 55) antigens is not of itself a reason for doubting the existence of the corresponding genes, which must, however, until such antigens are discovered, be regarded as recessive in their expression. Dominance and recessiveness are not, as the author implies (p. 16) immutable qualities of genes, but statuses which can be altered by the advance of knowledge.

While, therefore, the book can be recommended to those who are primarily interested in the clinical and immunological aspects of the blood groups, those who wish to gain an understanding of the genetical side may find it unnecessarily difficult. Even on the immunological side the book is somewhat eclectic and should not be treated as a complete practical guide.

A. E. MOURANT.

EYE MOVEMENTS AND READING

L'Electro-oculographie ou l'Enregistrement des Mouvements Oculaires. Son Application à l'Étude de la Lecture Normale et des Anomalies Pathologiques de la Lecture. By Viktor Kabersek. (Pp. 210; illustrated. No price.) Paris: R. Foulon. 1960

In this book, a doctoral thesis, M. Kabersek gives a very detailed account of the eye movements which occur during reading. His technique is to measure the electrical potential field about the eye, which alters as the eye rotates (electro-oculography). Brief reports have already been published (Rémond *et al.*), but this is the first detailed account of the technique and results. It is therefore disappointing that the findings are not so convincing as previously seemed to be the case.

In such a highly instrumented field technique is all-important, and in many respects M. Kabersek's methods are not ideal. The electrical potentials are recorded with multiple E.E.G. electrodes, placed rather far from the eyes. The small signals they record are further attenuated by a potentiometric device designed to enable horizontal and vertical eye movements to be recorded separately. The result is that (in those figures where calibrations are given) the sensitivity is less than 5 μV/degree of eye rotation—less than one-third of that obtained by other workers. This low sensitivity seems to have driven the author to use amplifiers of narrow band width (10 to about 30 cycles per second), which seriously distort the records. This is doubly unfortunate, since slow eye movements cannot be recorded at all, and artifacts are indistinguishable from eye movements. The author has gone to great pains to reconstruct eye movements from his records (scopograms), and believes that, since the reconstructions are internally consistent, artifacts do not occur. However, where the reader can judge for himself (Figs. 4, 11, 31, 53A) it is obvious that artifacts may influence the results.

Within these limitations a very detailed study of reading patterns has been made. Thirty subjects with primary education, twenty with secondary education, and seven with university education have been studied. Twenty-four different types of eye movement are distinguished and the frequency, speed, and amplitude of each type related to educational level. In brief, the author finds that the higher the educational level the more rapidly and accurately are reading movements made, but that there is less correlation between the speed of correction of reading errors and educational level. Many tables of results are given, but the statistical data are incomplete. This is a pity, since it seems that the author had applied t-tests to bimodal and strongly skewed distributions, so that the confidence limits quoted are not really relevant. In addition, several of the histograms are misdrawn.

In the final third of the book, the author deals with the abnormal reading patterns found in patients with disease as diverse as aphasia, G.P.I., and melancholia, and demonstrates a variety of novel applications for his technique—for example, the testing of colour blindness, and nystagmography. This part, if not critical, is most stimulating and would repay the attention of anyone working on the E.E.G.

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FRACTURES AND SOFT-TISSUE INJURIES

The Management of Fractures and Soft Tissue Injuries. By the Committee on Trauma, American College of Surgeons. Based on *An Outline of the Treatment of Fractures*, seventh edition, and *Early Care of Acute Soft Tissue Injuries*, second edition. (Pp. 372+xix; illustrated. 35s.) Philadelphia and London: W. B. Saunders. 1960.

Two well-known manuals previously published by the Committee of Trauma of the American College of Surgeons have now been revised and combined into one volume. Based upon the seventh edition of *An Outline of the Treatment of Fractures*, and the second edition of *The Early Care of Acute Soft Tissue Injuries*, this book provides guidance to those responsible for the early care of the injured.

The American College of Surgeons, through their Committee on Trauma, have produced an excellent composite edition and provided an up-to-date résumé of their views on the management of fractures and soft-tissue injuries. Their account is both authoritative and comprehensive, yet sufficiently brief to be complete in an almost pocket-sized edition of some 350 pages with only 61 illustrations.

As one would expect from its origin, the book is divided into two sections. The first is concerned with a synopsis of the treatment of fractures, and describes with laudable clarity not only the care of individual fractures but also the management of the injured patient from the moment of injury until complete recovery. Space is given to a brief description of the committee's views on the organization of an accident service; unfortunately, however, it is too brief to be of great value,

and an opportunity for guidance in this matter has been lost. It is refreshing to read in this section such statements as "the simplest and most efficient treatment of fractures is the old-fashioned method of manual reduction and immobilization by means of plaster of Paris." And "delayed union and non-union are frequently the result of violent or repeated attempts at reduction, inadequate reduction or insufficient and too short-lived immobilization of bone fragments. Open operations are a frequent cause of these complications."

Soft-tissue injuries, which include damage to the thorax, head, and abdomen, are well described in the second section. It is difficult to single out one chapter for praise because the standard is high throughout; however, we were particularly impressed by the common-sense description of shock, a section clearly written by a surgeon of considerable practical experience in this field.

We believe this to be a valuable book. We know of no similar work which provides the reader with such an excellent, brief, and practical account of the early management of the injured. Both casualty officers and those members of the public who ride motor-bicycles or drive recklessly should benefit from its publication.

H. OSMOND-CLARKE.
RODNEY SWEETNAM.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Haemophilic Diseases in Denmark. A Classification of the Clotting Defects in 78 Haemophilic Families. By Knud-Erik Sjølin, M.D. Translated from the Danish by Elisabeth Aagesen. (Pp. 349; illustrated. 35s.) Oxford: Blackwell Scientific Publications. 1961.

Leukocyte Agglutinins. Properties, Occurrence and Significance. By Sven-Age Killmann, M.D. (Pp. 95. 20s.) Oxford: Blackwell Scientific Publications. 1961.

Mortuary Science. By Frederick C. Gale. (Pp. 214+xxiii; illustrated. 76s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications Ltd. 1961.

Molecular Genetics and Human Disease. Edited by Lytt I. Gardner, M.D. (Pp. 297+xviii; illustrated. 92s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961.

A Text-Book of Midwifery. For Students and Practitioners. By R. W. Johnstone, C.B.E., M.A., M.D., Hon.LL.D., F.R.C.S.Ed., F.R.C.O.G., F.R.S.Ed. Eighteenth edition. (Pp. 592+xvi; illustrated. 45s.) London: Adam and Charles Black. 1961.

The Use of Isotopes in Haematology. By L. G. Lajtha, M.D., D.Phil. (Pp. 83+x; illustrated. 21s.) Oxford: Blackwell Scientific Publications. 1961.

The Neural Basis of Human Behavior. By Harold Saxton Burr, Ph.D. (Pp. 261+ix; illustrated. 60s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications Ltd. 1961.

Spiritual Therapy. How the Physician, Psychiatrist and Minister Collaborate in Healing. By Richard K. Young and Albert L. Meiburg. (Pp. 192. 15s.) London: Hodder and Stoughton. 1961.

Electron Microscopy. A Handbook for Biologists. By E. H. Mercer, D.Sc., Ph.D., and M. S. C. Birbeck, M.A. (Pp. 76+vi. 9s. 6d.) Oxford: Blackwell Scientific Publications. 1961.

Scientific Aspects of Neurology. Leeds Neurological Sciences Colloquium 1959-60. Edited by Hugh Garland, T.D., M.D., F.R.C.P. (Pp. 264+xi; illustrated. 50s.) Edinburgh and London: E. and S. Livingstone Ltd. 1961.

Atlas of Medical Mycology. By Emma Sadler Moss, B.S., B.M., M.D., and Albert Louis McQuown, B.S., B.M., M.D. Second edition. (Pp. 335+xi; illustrated. 88s.) London: Baillière, Tindall and Cox, Ltd. 1960.

Pharmacology. The Nature, Action and Use of Drugs. By Harry Beckman, M.D. Second edition. (Pp. 805×xvii. £5 8s. 6d.) Philadelphia and London: W. B. Saunders Company. 1961.

Specifications for Pesticides. Insecticides, Rodenticides, Molluscicides, Herbicides, Auxiliary Chemicals, Spraying and Dusting Apparatus. Second edition. (Pp. 523. £2 10s.) Geneva: World Health Organization. London: H.M. Stationery Office. 1961.

Angiography. Edited by Herbert L. Abrams, M.D. Volumes 1 and 2. (Pp. 461×xvi; illustrated. Pp. 465–807+vii; illustrated. £17.) London: J. and A. Churchill Ltd. 1961.

The Premature Baby. By V. Mary Crosse, O.B.E., M.D. (Lond.), D.P.H., M.M.S.A., D.Obst.R.C.O.G. Fifth edition. (Pp. 266+viii; illustrated. 24s.) London: J. and A. Churchill Ltd. 1961.

The Physiological Basis of Medical Practice. Edited by Charles Herbert Best, C.B.E., M.A., M.D., D.Sc.(Lond.), F.R.C.S., F.R.C.P.(Canada), and Norman Burke Taylor, V.D., M.D., F.R.S.(Canada), F.R.C.S.Ed., F.R.C.P.(Canada), M.R.C.S.(Eng.), L.R.C.P.(Lond.). Seventh edition. (Pp. 1,552+xxvi; illustrated. No price.) London: Baillière, Tindall and Cox, Ltd. 1961.

Medical Entomology. By William B. Herms, Sc.D. Revised by Maurice T. James, Ph.D. Fifth edition. (Pp. 616+xi; illustrated. 87s. 6d.) New York: The Macmillan Company. 1961.

A Sociological Contribution to the Understanding of Aggression and its Treatment. Based upon Social Research performed at Netherne Hospital, Coulsdon, Surrey. By M. S. Folkard, Ph.D., B.Sc.(Soc.). Foreword by R. K. Freudenberg, M.D., D.P.M. (Pp. 176+ix. 7s. 6d.) Coulsdon, Surrey: Netherne Hospital. 1961.

Pathology. A Dynamic Introduction to Medicine and Surgery. By Thomas Martin Peery, M.D., and Frank Nelson Miller, jun., M.D. (Pp. 626+vii. 40s.) London: J. and A. Churchill Ltd. 1961.

The Newborn Child. By David G. Vulliamy, M.D., M.R.C.P., D.C.H. (Pp. 163+vii; illustrated. 15s.) London: J. and A. Churchill Ltd. 1961.

Progress in Clinical Surgery. By various authors. Edited by Rodney Smith, M.S., F.R.C.S. Series II. (Pp. 327+ix; illustrated. 50s.) London: J. and A. Churchill Ltd. 1961.

The Art of Administration. By A. Leslie Banks, M.A., M.D., F.R.C.P., D.P.H., and J. A. Hislop, M.A., M.D., F.R.C.P.Ed. (Pp. 224. 12s. 6d.) London: University Tutorial Press Ltd. 1961.

Biology of Pyelonephritis. Editors: Edward L. Quinn, M.D., F.A.C.P., and Edward H. Kass, M.D., Ph.D., M.A.(Hon.), F.A.C.P. (Pp. 708+xxiv; illustrated. £6 10s.) London: J. and A. Churchill Ltd. 1961.

Progress in Medicinal Chemistry. Volume 1. Edited by G. P. Ellis, B.Sc., Ph.D., F.R.I.C., and G. B. West, B.Pharm., D.Sc., Ph.D. (Pp. 262+ix; illustrated. 60s.) London: Butterworths. 1961.

Progress in Medical Virology. Edited by E. Berger and J. L. Melnick. Volume 3. (Pp. 496; illustrated. Sw. Fr. 80.) Basle and New York: S. Karger. 1961.

Physiological Responses to Hot Environments. M.R.C. Special Report Series No. 298. An account of work done in Singapore, 1948–1953, at the Royal Naval Tropical Research Unit, with an appendix on preliminary work done at the National Hospital for Nervous Diseases, London. Compiled by R. K. Macpherson. (Pp. 323+xv. 35s.) London: H.M. Stationery Office. 1960.

A Syllabus of Laboratory Examinations in Clinical Diagnosis. Critical Evaluation of Laboratory Procedures in the Study of the Patient. Revised edition. Edited by Lot B. Page, M.D., and Perry J. Culver, M.D. (Pp. 580+xxiv. 60s.) London: Oxford University Press. Cambridge, Mass.: Harvard University Press. 1960.

Die Chirurgische Behandlung der Angeborenen Fehlbildungen. Edited by Priv.-Doz. Dr. K. Kremer. (Pp. 592+xvi; illustrated. DM. 118.) Stuttgart: Georg Thieme Verlag. 1961.

Quaestionarium Medicum in English, French, Italian, Spanish, Portuguese, German, Dutch, Norwegian, Swedish, Finnish, Polish, Russian, Greek, Chinese, Japanese, Malay, Esperanto. By F. Meyboom. (Pp. 213+vii. 30s.) Amsterdam, London, New York, Princeton: Elsevier Publishing Company. 1961.

Your Bread and Your Life. By Doris Grant. (Pp. 243. 13s. 6d.) London: Faber and Faber. 1961.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY MAY 6 1961

PRONE OR SUPINE?

Recent work has suggested that whether a young infant is placed in the prone or supine position for his sleep may be of practical importance. Some years ago Australian and other workers[1-4] suggested that sleeping prone led to faulty alignment of feet, and even that moulded cardboard splints should be attached to the extensor surfaces of the knees to maintain extension and so prevent prone sleeping. There has been some recent support for this view.[5] American workers[6] compared the respiration rate of 119 premature and 49 full-term infants in the prone and supine positions, and found that in premature babies it was significantly higher in the prone than in the supine position, but that the difference decreased with increasing weight and age. Respirations of regular rate and amplitude were characteristic of the premature baby in the prone position, while phasic respiration, with irregularity of rate and amplitude, was noted in the supine position, and the amplitude of respiration was greater. It was thought that the reason for the lower incidence of periodic breathing in those babies with the more rapid respirations (the prone group) might be related to the increased minute volume of respiration. In the supine position the intercostal and abdominal muscles can more freely assist the diaphragm with each respiratory movement, but in the prone position the abdominal and intercostal muscles are compressed against the surface of the crib and cannot assist the diaphragm in the respiratory activity. It is a matter of opinion whether from this point of view the supine position is better than the prone for the young premature baby.

There is virtually no risk of suffocation when babies are placed in the prone position—provided, of course, there is no pillow. Consequently, owing to its several advantages, there is an increased tendency in the United States to place infants in this position for their naps and sleeps. In the first place, the risk of inhaling vomit is decreased. A. M. N. Gardner,[7] in Great Britain, wrote that when there is a tendency to vomit a prone or semiprone position is the only safe one for a comatose or weak patient. His work applied to older children and adults, but it presumably applies to premature babies as well, and he refers to this in his paper. More recently the relative incidence of napkin rash, excoriation of the skin by scratching, and of crying was studied in a controlled experiment in which infants were chosen in rotation to sleep in the prone and supine positions.[8] There was twice as much crying in the supine position, with more napkin rashes and more skin excoriations. When the position of the infants who were crying was reversed, one-half of the infants on their backs stopped crying when placed in the prone whereas only an occasional infant crying in the prone position stopped crying when placed on his back. Of 141 infants in the prone position, two had chafing of the skin of the knees, and, of 140 on the back, two had chafing of the skin of the heels.

The current American practice of nursing infants in the prone position has led to interesting developmental changes. K. S. Holt,[9] after special experience with the Gesell method of examination of babies in England, studied 82 infants at Iowa, and compared their motor development in the prone and supine positions with that seen in England. He found that the Iowa babies accustomed to sleeping prone tended to show more advanced motor development when in the prone position, but to be relatively retarded when supine. The American mothers thought that their infants were more comfortable when prone, that the risk of inhalation of vomit was less, that they got their wind up more easily, that the position strengthened the back, made the head a better shape, and helped their colic. It has long been known that infants with evening colic (three-months colic) are more comfortable in the prone position,[10] especially if some pressure is placed on the abdomen.

It may be argued that infants put in either the prone or the supine position will roll into the position which they prefer. This is not true of younger infants. The average age at which infants begin to roll completely over from the prone to the supine is about 5 months, and from the supine to the prone about 6 months. It would seem that there is scope for more observation on the relative advantages of the prone and supine positions for infants.

[1] Macnamara, J., *Med. J. Australia*, 1947, **2**, 720.
[2] —— ibid., 1948, **2**, 592.
[3] Thelander, H. E., and Fitzhugh, M. L., *J. Pediat.*, 1942, **21**, 306.
[4] Zeiss, F. R., *Pediat. Clin. N. Amer.*, 1955, November, p. 957.
[5] Auerbach, S. P., ibid., 1961, **8**, 225.
[6] Kravitz, H., Elegant, L., Block, B., Babakitis, M., and Lundeen, E., *Pediatrics*, 1958, **22**, 432.
[7] Gardner, A. M. N., *Quart. J. Med.*, 1958, **27**, 227.
[8] Keitel, H. G., Cohn, R., and Harnish, D., *J. Pediat.*, 1960, **57**, 884.
[9] Holt, K. S., ibid., 1960, **57**, 571.
[10] Illingworth, R. S., *Arch. Dis. Childh.*, 1954, **29**, 165.

DIAGNOSIS OF TUBERCULOUS MENINGITIS

Several factors have combined to reduce the incidence of tuberculous meningitis in recent years, including better social conditions, more intensive public health measures, the prophylactic treatment of primary tuberculous infections with antituberculous drugs, and giving B.C.G. inoculation to the newborn in some of our large cities. None the less, cases of this disease continue to be admitted to our hospitals, and sometimes the powerful weapons now available to deal with them are blunted by a regrettable delay in diagnosis. It is difficult for younger doctors to appreciate the changes that have occurred since the introduction of streptomycin in 1946, before which time a diagnosis of tuberculous meningitis was equivalent to a death warrant. The importance of early diagnosis now that treatment is available with streptomycin, isoniazid, *p*-aminosalicylic acid, and steroids is well substantiated.[1–6] Patients treated late in the disease still often die and the survivors are often left with such gross neurological damage that death might seem a preferable outcome.

These facts have recently been stressed again by Edith Lincoln and her colleagues in New York,[7] and they have published a useful review of the diagnostic problems. Patients requiring treatment for tuberculous meningitis may be grouped into those diagnosed in the early, medium, and advanced stages of the disease.[1] The common presenting features in the early stage are fever, vomiting, and apathy. These are common symptoms in childhood, but tuberculous meningitis should be suspected when no other adequate cause can be found, and especially if irritability is combined with periods of drowsiness. Constipation is almost invariable and often severe. Signs of meningeal irritation, such as neck stiffness, are usually absent. The young child rarely complains of headache. Infrequently the disease is heralded by a convulsion. It will be clear that early diagnosis must depend on the doctor's suspicions being aroused. A history of contact with a known case of tuberculosis is obviously of great significance and should always be sought. A recent history of measles or minor head injury is also to be regarded as suggestive.[7] When suspicion has been awakened, a tuberculin skin test should be performed. A negative result is rare in the early stage of the disease, whereas a positive test in a young child is highly significant. Ophthalmoscopy may reveal choroidal tubercles, especially when there is an associated miliary tuberculosis. A chest radiograph may show a primary complex or the "snowstorm" appearances of miliary tuberculosis, but a normal film by no means precludes the diagnosis. Lincoln and her co-workers[7] stress that signs of mild upper respiratory infection are not rare and do not negative the diagnosis, especially when fever, lethargy, and irritability seem out of proportion in their severity.

In the middle stage of the disease specific neurological signs make their appearance. Slight nuchal rigidity is common, a positive Kernig's sign somewhat rare. Cranial-nerve palsies, spasticity, and early blurring of consciousness should always be regarded urgently and their cause determined. The sense of urgency is particularly necessary in the child of under 3 years, because the advanced stage of the disease may be reached with frightening rapidity. At this stage the child is semi-comatose. Head retraction and a positive Kernig's sign are common and so also is decerebrate rigidity. A crackpot sound on percussion of the skull and frank papilloedema are other signs of late appearance in most instances. Patients who recover from the advanced stage of the disease show various permanent neurological sequelae such as hydrocephalus, blindness, deafness (rare in the absence of intrathecal streptomycin), spastic palsies, and mental deficiency.

Confirmation of the diagnosis must be obtained in hospital by examination of the cerebrospinal fluid. It is just as imperative that the hospital physician should be imbued with the same sense of urgency in the diagnosis as his colleague in general practice. The C.S.F. will be clear or slightly opalescent; the cell count is raised (50–500 per c.mm.), and lymphocytes predominate over polymorphonuclears. These findings are sufficient to exclude pyogenic meningitis which has been altered by antibiotics given before admission, but similar results may be encountered in virus infections of the central nervous system. Highly relevant information in this differential diagnosis may be found in the history, which in virus infections is usually of a much more sudden onset, or in evidence of tuberculosis, such as a history of contact, a positive skin test, positive chest radiograph, or choroidal tubercles. In tuberculous meningitis the sugar content of the C.S.F. is reduced (below 50 mg. per 100 ml.) in about 90% of early cases, a finding that excludes virus meningitis. The protein content tends to be considerably higher in tuberculous cases (above 50 mg. per 100 ml.). The chloride content falls too late in the disease to be of much diagnostic importance. Direct examination of

[1] Medical Research Council, *Lancet*, 1948, **1**, 582.
[2] Lorber, J., *Amer. Rev. Tuberc.*, 1954, **69**, 13.
[3] —— *Brit. med. J.*, 1956, **1**, 1009.
[4] —— Ibid., 1960, **1**, 1309.
[5] Fyfe, W. M., *Arch. Dis. Childh.*, 1959, **34**, 334.
[6] Miller, F. J. W., *Recent Advances in Paediatrics*, 1958, 2nd ed., edited by D. Gairdner. London.
[7] Lincoln, E. M., Sabato, V. R., Sordillo, M. D., and Davies, P. A., *J. Pediat.*, 1960, **57**, 807.

the fluid may reveal acid-fast bacilli in centrifuged deposit or the pellicle which forms when it is allowed to stand overnight. Culture is not helpful to early diagnosis, though it later provides valuable confirmation. It is, fortunately, only infrequently that the differential diagnosis of tuberculous meningitis and the virus infections proves to be a serious problem.

SOBERING-UP

Rapid sobering-up from the drunken state may often be desirable for clinical or social reasons, but it is not easily achieved, and the diverse therapeutic methods that have been suggested are mostly of disputed value. The inhalation of carbon dioxide and oxygen has been reported to relieve symptoms of intoxication and to accelerate the fall of blood alcohol[1-3] (presumably by increased excretion through the breath). These findings have been criticized by H. W. Newman and J. Card,[4] who found that the fall of blood alcohol with this treatment was transient only, while a recent contribution[5] from Sydney reports no discernible sobering effects from the inhalation of 5% carbon dioxide in oxygen by a single subject in a controlled experiment. There is general agreement, however, that carbon dioxide and oxygen are helpful in the treatment of patients in alcoholic coma. The rate of disappearance of alcohol from the body is constant and is not affected by exercise[6 7]; indeed, R. N. Harger and H. R. Hulpieu[8] have concluded that this rate cannot be materially changed by any means not harmful to the body. A. Pletscher[9] and T. M. Carpenter[10] reported that the giving of fructose accelerated the elimination of alcohol, but F. Heim[11] challenged these findings. O. Martensen-Larsen[12] has advocated fructose as Danish honey, two divided doses of 125 g. each, to produce a transient disulfiram-like reaction with sleep and subsequent sobriety, and also a mixture of disulfiram, sodium chloride, and an antihistamine in specified proportions.[13]

V. P. Wordsworth[14] reported favourably on the use of pyridoxin (vitamin B_6), 100 mg. intravenously, for drunkenness with excitement, but other work has not supported these claims.[15 16] J. Gould[17] claims that "social protection" may be obtained by taking 200–600 mg. ascorbic acid and 100–200 mg. thiamine by mouth before and after a drinking-bout and again next morning. He also advocates[18] giving high doses of vitamin-B complex and ascorbic acid intravenously when intensive therapy is required. Insulin and glucose have been found of value in treating acute intoxication,[19 20] while there is some experimental evidence[21] to suggest that pyruvate[20] radically increases the metabolism of alcohol. A recent and particularly interesting contribution from M. Goldberg and colleagues[22] reports the treatment of acute alcoholism with intravenous L-triiodothyronine. In a series of twelve patients (mostly chronic alcoholics) the mean rate of metabolism of alcohol was doubled, and the odour of alcohol in breath disappeared in two hours as compared with 6–10 hours in untreated controls. A.C.T.H. and adrenocortical hormones are said to be useful in preventing delirium tremens.[23 24]

In practice, treatment of a case of alcoholic intoxication begins by emptying the stomach, unless there has been recent vomiting. Excitement may be best relieved by intramuscular promazine or chlorpromazine, while if a hypnotic is required glutethimide is preferable to barbiturates. Incipient delirium tremens calls for hospital care. When restless addictive craving needs to be relieved, sublingual apomorphine deserves a trial. Large doses of vitamin-B complex intravenously may do good, are unlikely to do harm, and have the advantage of being suitable for patients who need to remain ambulant. When the patient's reactions are distinctly slowed and he has a task to perform, amphetamine by mouth is justifiable on an isolated occasion.

Despite some promise from recent work,[22] it must be admitted that, at present, there is no certain way of rendering a drunken man sober and socially competent much sooner than he would otherwise become. The greatest caution should be exercised when an intoxicated person asks to be made fit to drive, for treatment directed to this end might, even if apparently beneficial, have unfortunate medico-legal sequelae in the event of subsequent mishap on the road. The medical practitioner approached with such a request should give sobering-up treatment only with the proviso that the patient makes other arrange-

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2 Robinson, L. J., and Selesnick, S., *J. Amer. med. Ass.*, 1935, **105**, 1734.
3 McFarland, R. A., and Barach, A. L., *Amer. J. med. Sci.*, 1936, **192**, 186.
4 Newman, H. W., and Card, J., *J. Amer. med. Ass.*, 1936, **108**, 595.
5 Hansman, F. S., and Marshall, S. V., *Med. J. Aust.*, 1960, **2**, 857.
6 Carpenter, T. M., Lee, R. C., and Burdett, M., *Amer. J. Physiol.*, 1933, **105**, 17.
7 Nyman, E., and Palmlov, A., *Skand. Arch. Physiol.*, 1934, **68**, 271.
8 Harger, R. N., and Hulpieu, H. R., in *Alcoholism*, edited by G. N. Thompson, 1956, Springfield, p. 152.
9 Pletscher, A., Bernstein, A., and Staub, H., *Quart. J. Stud. Alcohol*, 1953, **14**, 312 (abstract).
10 Carpenter, T. M., and Lee, R. C., *J. Pharmacol. exp. Ther.*, 1937, **60**, 286.
11 Heim, F., *Arch. exp. Path. Pharmakol.*, 1952, **216**, 183.
12 Martensen-Larsen, O., *Brit. med. J.*, 1954, **2**, 464.
13 —— *Quart. J. Stud. Alcohol*, 1953, **14**, 408.
14 Wordsworth, V. P., *Brit. med. J.*, 1953, **1**, 935.
15 Berg, S., *Med. Klin.*, 1954, **49**, 1037.
16 Abele, G., *Dtsch. Z. ges. gerichtl. Med.*, 1956, **44**, 717.
17 Gould, J., *Proc. roy. Soc. Med.*, 1954, **47**, 217.
18 —— in *Recent Progress in Psychiatry*, Vol. III, edited by G. W. T. H. Fleming and A. Walk, 1959, London.
19 Goldfarb, W., Bowman, K. M., and Parker, S., *J. clin. Invest.*, 1939, **18**, 581.
20 Thimann, J., and Peltason, P., *Quart. J. Stud. Alcohol*, 1947, **7**, 506.
21 Westerfeld, W. W., Stotz, E., and Berg, R. L., *J. biol. Chem.*, 1942, **144**, 657.
22 Goldberg, M., Hehir, R., and Hurowitz, M., *New Engl. J. Med.*, 1960, **263**, 1336.
23 Smith, J. J., *Quart. J. Stud. Alcohol*, 1950, **2**, 190.
24 Voegtlin, W. L., ibid., 1953, **14**, 28.
25 Hoover, M. P., *Canad. med. Ass. J.*, 1960, **83**, 1352.
26 Cummins, J. F., and Friend, D. G., *Amer. J. ment. Sci.*, 1954, **227**, 561.
27 Memorandum on Alcoholism. *Brit. med. J. Suppl.*, 1961, **1**, 190.

ments for his journey. When the patient is a victim of chronic alcoholism, treatment of acute intoxication may be used to pave the way for later long-term treatment,[25] and we may agree with J. F. Cummins and D. G. Friend[26] that in these circumstances "the management of the patient has only just begun." This part of the problem is the subject of an important memorandum prepared by the Joint Committee of the B.M.A. and the Magistrates' Association,[27] and published recently.

IDIOPATHIC RETROPERITONEAL FIBROSIS

Reports of ninety-five patients in whom the ureters had been obstructed by a retroperitoneal fibrosis of unknown cause have recently been reviewed by J. K. Ormond.[1] He had himself described the first two cases in 1948, and though subsequent reports have added little information about the aetiology of the disease they have drawn attention to a cause of hydronephrosis which can be relieved if recognized and treated before the kidney is irreparably damaged. The essential pathological process is a dense, almost keloid, fibrosis in the retroperitoneal tissues by the lower half of the abdominal aorta and spreading outwards to envelop one or both ureters. A similar type of fibrosis may occur in the mediastinum, and the same patient may have both mediastinal and abdominal lesions.[2]

The indefinite early symptoms include backache, abdominal discomfort, and slight frequency of micturition, and most of the patients look sufficiently ill to require special investigations. As the ureteric obstruction increases, renal pain, oliguria, and finally anuria may supervene. The anuria often comes as a surprise, and may occur within a few weeks of taking a normal intravenous pyelogram. When ureteric obstruction is more gradual, uraemic symptoms predominate. Compression of the vena cava, aorta, and iliac vessels may cause oedema of the legs or claudication.

The clinical examination helps little in the diagnosis, but there may be a palpable tender kidney, a few cells in the urine, and occasionally a raised erythrocyte sedimentation rate. F. P. Raper[3 4] pointed out that the pyelograms, of necessity retrograde if renal function is poor, show a characteristic finding which should suggest the diagnosis. Typically there is a bilateral hydronephrosis with obstruction of the middle third of the ureters, and at the point of obstruction the ureters are drawn towards the mid-line. Sometimes one ureter is completely obstructed and then the kidney will not be functioning. Though the patient may have developed anuria it is still usually possible to pass a ureteric catheter up the most recently obstructed ureter, and this may be helpful in treating the uraemic patient.

Once uraemia is controlled, direct treatment of the ureteric obstruction should be attempted and is very often successful. Raper has reviewed available methods, and these include ureterolysis, excision, and re-anastomosis of the ureter or even replacement of the ureter by small intestine. A nephrostomy may be needed at some stage. Cortisone has been given to a few patients to reduce the fibrosis, sometimes with great benefit. The important point is that a new disease has been recognized, and it can usually be treated successfully.

[1] Ormond, J. K., *J. Amer. med. Ass.*, 1960, **174**, 1561.
[2] Riches, E., *J. roy. Coll. Surg. Edinb.*, 1959, **5**, 22.
[3] Raper, F. P., *Brit. J. Urol.*, 1956, **28**, 436.
[4] —— *Proc. roy. Soc. Med.*, 1960, **53**, 690.

PARENTAL CONSENT TO TREATMENT

A little over a year ago reference was made in these columns[1] to a plan by the Sheffield Regional Hospital Board to set up juvenile courts in hospitals if the parents refused to give consent to an operation urgently needed by their child. More recently,[2] we reported an instance where such a plan was effectively used to place into the care and protection of a local authority a rhesus-positive baby whose father, a Jehovah's Witness, refused to consent to the performance of a blood transfusion: the local authority then gave consent to the transfusion.

The Minister of Health has now advised[3] hospital authorities not to resort to this procedure in such cases. He appears to have given that advice largely in response to pressure from local authorities and clerks to justices. A recent letter from the Ministry to secretaries of regional hospital boards concludes:

> Boards will be generally aware that in the past problems of this kind have been resolved by the doctor deciding his course of action by the dictates of his individual professional conscience. When advice has been sought it has been given on the lines that, if the doctor gets a written supporting opinion from a colleague that the patient's life is in danger if operation or transfusion is withheld and gets an acknowledgment (preferably in writing) from the parent or guardian that he refuses consent despite the explanation of the danger given to him by the doctor, he runs little risk in a court of law if he acts with due professional competence and according to his own professional conscience."

The problem has been considered by the Joint Committee of the B.M.A. and the Magistrates' Association, and its conclusions were accepted by the Council, whose annual report contains the following passage[4]: "The number of cases where there is only one accepted method of treatment, and where such treatment has to be given urgently as a matter of life and death, is relatively small. In the Council's view, a doctor's first consideration will necessarily be the health of his patient, irrespective of his own position in law."

The Joint Committee thought there was a need for a simpler and more direct procedure, limited to cases where the operation to which consent has been refused is a matter of life and death, and the Councils of both the B.M.A. and the Magistrates' Association have requested the Home Secretary to ask the Criminal Law Revision Committee to consider at an early date the possibility of amending legislation to deal specifically with cases where parental consent to a life-saving

[1] *Brit. med. J.*, 1960, **1**, 943.
[2] Ibid., 1960, **2**, 1320.
[3] *Hansard*, 1961, **637**, No. 82, col. 97.
[4] *Brit. med. J. Supplement*, 1961, **2**, 186.

operation on a child is refused. Whether such legislation will be forthcoming is perhaps doubtful.

It is probable that a doctor who acts competently and in good faith in such a situation (even without using the "care and protection" procedure) will find protection under the common law. Even if an operation without the parents' consent in such cases is a technical assault (which is open to question) it is unlikely that any damage to the child could be proved, and the verdict would be at the most for nominal damages save in exceptional cases. The question of liability at common law is an interesting one which is examined elsewhere in this issue (p. 1327).

TOXINS AND ANTITOXINS IN BURNED PATIENTS

Until about twenty-five years ago the severe illness and death of badly burned patients were commonly attributed—in part, at least—to "toxins" formed in the damaged tissues and absorbed into the blood-stream. Treatment with tannic acid was introduced in the belief that it would fix such toxins by precipitating them in the burns and thus prevent their absorption.[1] But although various potentially toxic substances have been found in burned tissue, the evidence about their importance as a cause of the illness associated with burns has been inadequate. When the serious effects of fluid loss, infection, kidney damage, anaemia, and metabolic disturbance were demonstrated, it seemed that these factors were quite enough to account for the clinical features of injury from a burn, and interest in the hypothesis of toxaemia waned. But in spite of improvements in fluid and electrolyte control, skin grafting, and antibiotic therapy, mortality from severe burns did not fall appreciably after about 1945.[2]

The current revival of interest in the toxaemia of burns owes something to these disappointments in the modern treatment of the severely burned, and its emphasis is on the prophylactic and therapeutic possibilities of antibodies produced in burned patients. N. A. Feodorov and his colleagues[3 4] in Moscow claim to have found in the serum of burned dogs complement-fixing antibodies which reacted with extracts of burned skin of dogs. On the basis of these and other animal studies they have tested and reported favourably on the treatment of severely burned patients with infusions of serum or plasma from patients who have recently recovered from burns. In Chicago, S. R. Rosenthal,[5 6] whose work in this field goes back to 1937, has recently reported that the growth of HeLa cells suspended in Eagle's medium was inhibited by the serum of recently burned or severely injured persons, and that the inhibition could be prevented by the addition to the culture of serum from patients who had recovered from burns. Rosenthal claims some promising results in a few severely burned patients treated with serum from recovered cases. In Prague, M. Dobrkovsky and his colleagues[7] have reported that the serum of recently burned subjects contained antibodies which caused agglutination of collodion particles sensitized with extracts of burned tissues.

These observations are of great interest, and are consistent in claiming the demonstration of an immune response to burned tissue. The arrival at a common opinion by different techniques may be thought to reinforce the claims put forward, but there are some differences and many uncertainties in the interpretation of the results. Even if the presence of an antibody is established, its value in the treatment of burned patients still remains to be proved. The antigen cannot be assumed to act as a toxin. The antibody cannot be assumed to benefit the patient, and if it is a true auto-antibody its presence might actually be harmful. If, on the other hand, infusion with convalescent serum can be shown to benefit burned patients, this effect may be due —partly or entirely—to antibacterial antibodies which appear in the circulation after severe burns and which may have a protective action.[8 9] Further detailed study of these problems is needed.

[1] Davidson, E. C., *Surg. Gynec. Obstet.*, 1925, **41**, 202.
[2] Bull, J. P., and Fisher, A. J., *Ann. Surg.*, 1954, **139**, 269.
[3] Feodorov, N. A., *Proc. 6th Congr. Internat. Soc. Blood Transf.*, 1956, p. 44.
[4] —— *Abstr. 1st Internat. Congr. Research in Burns*, Washington, 1960, p. 41.
[5] Rosenthal, S. R., *Ann. Surg.*, 1937, **106**, 257.
[6] —— Hartney, J. B., and Spurrier, W. A., *J. Amer. med. Ass.*, 1960, **174**, 957.
[7] Dobrkovsky, M., Dolezalova, J., and Pavkova, L., *Abstr. 1st Internat. Congr. Research in Burns*, 1960, p. 43.
[8] Fox, J. E., and Lowbury, E. J. L., *J. Path. Bact.*, 1953, **65**, 519, 533.
[9] Millican, R. C., *Abstr. 1st Internat. Congr. Research in Burns*, Washington, 1960, p. 57.

NEW GROUP TO STUDY DIABETES

In April, 1960, the British Diabetic Association set up a Medical and Scientific Section. Previously the association was concerned more with the social and administrative aspects of diabetes than with the scientific. It had supported research, with fruitful results, but apart from the Annual Banting Memorial meetings it did not provide a forum for discussion for the clinicians and scientists interested in diabetes. Consequently many clinicians and laboratory workers thought that they did not see enough of each other when discussing problems of diabetes. It was therefore important that from the first the structure of the new Section should reflect this wish for a closer union, and it has happily done so by the election of Professor F. G. Young, F.R.S., the distinguished biochemist, as chairman, and Drs. J. M. Stowers and D. A. Pyke, experienced clinicians, as joint secretaries. That the balance of the new Section will be even was fittingly confirmed by the election of Dr. R. D. Lawrence as its honorary president at the first annual meeting held on April 7–8, for in his own career Lawrence has combined just those qualities which the Section is trying to apply to the new problems of diabetes.

In a recent talk[1] to the Historical Society of King's College Hospital Lawrence described how very many years ago a chip of bone flew into his eye while he was dissecting a mastoid; how, becoming infected, it led to the diagnosis of diabetes, which was then virtually a death sentence on a young man; how he went to

[1] To be published in the *King's College Hospital Gazette*.
[2] *Brit. med. J.*, 1961, **1**, 1168.

Florence to " tease out " his remaining months ; how Dr. Harrison, having tried the new insulin and found that " it worked," telegraphed him to come home at once ; and how Lawrence returned, sceptical and weary of trying many useless remedies, with results which we all know and rejoice in.

At the recent meeting three new members were elected to the committee—Professors Russell Fraser and W. J. H. Butterfield, whose departments are much concerned with metabolic problems of diabetes, and Dr. John Malins, whose unit at Birmingham has made considerable contributions to its description and management. The many interests so strongly represented in the Section augur well for its success. That it should prosper is important, for diabetes is still a serious menace to health and is the commonest cause of blindness in young people. Research into it is particularly active at present, as is evident from the work reported at the recent meeting.[2] It included Vallance-Owen's stimulating suggestion that the basic fault in diabetes is an excess of albumin-bound antagonist of insulin and that patients become fat because they are diabetic, not vice versa ; Ehrlich and Randle's studies on level of growth hormone in diabetes, prediabetes, and pregnancy ; and Oakley and Peel's report of their results in the treatment of diabetic pregnant women, showing that they have reduced the foetal loss to about 10% and have found that with improved diabetic control there has been a reduction of foetal and placental birth weights.

HEREDITY AND RENAL CALCULI

Fairly clear-cut methods of Mendelian inheritance underlie abnormal metabolic processes causing several types of renal calculi. For example, in primary hyperoxaluria there is good evidence for the operation of a recessive character.[1] In cystinuria the situation is similar though more complicated, since there is more than one genetically determined variety.[2 3] In renal tubular acidosis, where calcium is lost because of the renal secretion of acid metabolites, a family has been described in which the inheritance is probably controlled by a dominant gene. In gout, also, a dominant form of heredity is generally present, and occasionally small orange calculi are found in the renal calices.[4] Uric-acid stones are sometimes found independently of gout, but there appear to be no genetic studies of this type of lithiasis.[5]

Usually the cause of the stone is unknown, or we attribute it to environmental factors such as immobilization, dehydration, and infection, or to " non-genetic " diseases—for example, hyperparathyroidism among many—with which calculi are known to be associated. Since patients suffering these environmental and other hazards do not always develop calculi, there must be other agents responsible for their formation. Recently Mary G. McGeown[6] has made a good case for supposing that one of them is genetic. She investigated the family histories of 174 patients with calcareous calculi (cases with cystine or uric-acid calculi were excluded), and compared them with a similar number of controls matched for age and sex. She subdivided her information according to whether the parents, sibs, or offspring had calculi. Of the 348 parents, 16 were affected compared with 1 in the controls. Among the sibs there were 15 affected compared with 4 in the controls, and among the offspring 5 were affected against 1 in the controls. The probability of the differences among the parents and the sibs arising by chance is very low, but among the offspring the numbers are too small for an accurate analysis to be made.

McGeown found no relationship between a positive family history and the amino-acid pattern in the urine or the urinary excretion of calcium or the serum phosphorus (after excluding patients with hyperparathyroidism). Furthermore, she found that the incidence of a positive family history of stone was similar among patients with or without hyperparathyroidism. But an increased value for the ratio of phosphate and creatinine clearances did tend to be correlated with a positive family history.

An important finding in McGeown's investigation is the tendency (though not statistically significant) for the parent/offspring correlation to be greater than that of the sib/sib correlation. This bears out the hypothesis that a genetic factor is at work rather than an environmental one, because sibs are more likely to be brought up in the same environment than are parents and their offspring. If there were no correlation between spouses this would be further evidence against environmental factors.

An attractive hypothesis[7 8] is that the basic disorder in calculus formation relates to mucopolysaccharide metabolism, the mucoproteins forming a matrix to which calcium can be bound to form an insoluble complex. Though the blood-group substances probably contribute only a small part to the total mucoprotein in the urine[9] it would be worth while investigating this in some detail, since the presence of these substances in the body fluids (urine included) is genetically determined, " secretion " being dominant to " non-secretion." It is therefore possible that individuals with different mixtures of blood-group substances in their urines have a different liability to form calculi.

[1] Scowen, E. F., Watts, R. W. E., and Hall, E. G., *Ann. hum. Genet.*, 1958–9, **23**, 367.
[2] Harris, H., *Brit. med. Bull.*, 1957, **13**, 26.
[3] Harrison, A. R., *Postgrad. med. J.*, 1958, **34**, 163.
[4] Copeman, W. S. C., *Textbook of the Rheumatic Diseases*, 1955, 2nd ed., Livingstone, Edinburgh.
[5] Sorsby, A., *Clinical Genetics*, 1953, Butterworth, London.
[6] McGeown, M. G., *Clin. Sci.*, 1960, **19**, 465.
[7] Boyce, W. H., Garvey, F. K., and Norfleet, C. M., *Amer. J. Med.*, 1955, **19**, 87.
[8] ——, ——, ——, *Exp. Med. Surg.*, 1954, **12**, 450.
[9] Hartmann, G., *Group Antigens in Human Organs*, 1941, Munksgaard, Copenhagen.

The half-yearly indexes to Volume 2 of the *Journal* and *Supplement* for 1960 are now being dispatched. Members who have not previously asked for the indexes to be sent regularly to them can obtain copies, post free, from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1.

RECENT ADVANCES IN X-RAY TELEVISION

WITH SPECIAL REFERENCE TO UROLOGY

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Since the previous reports (Hanley, 1955, 1956; Greenwood, 1956, 1957) we have had five further years' experience with various forms of *x*-ray intensification, and it is becoming possible to assess the routine clinical value as opposed to the academic interest value of the various procedures and possibilities when applied to urology.

The relative advantages of the various types of apparatus depend upon the clinical information we require. For the urologist, the ability to watch the movements of the pelvis and ureter has opened up a new vista of clinical investigation, and one cannot now contemplate retrograde pyelography without visual control. However, not all of the types of apparatus available are of equal value to the urologist whatever the radiologists may think, and certain basic requirements are necessary.

Firstly, viewing of the screen or monitor must be binocular and two or more persons must be able to view simultaneously. It is not sufficient for the urologist to be told what the radiologist sees—he must be able to see for himself. Secondly, this viewing must be possible without acrobatics. The original monocular eyepiece was unsatisfactory in both respects. The size of the field is also important, because, although in principle the smaller the field the better the definition, it is very useful to have a large field for rapid localization before coning down on specialized areas. The field of the Marconi orthicon system can include both kidneys simultaneously if required.

The next essential is that it must be possible to take "spot films" of the area localized on the screen with the minimum of delay or alteration of the apparatus. Lastly, the apparatus must be easily accessible for the urologist and an anaesthetized patient.

Whereas five years ago only two makes of intensifier tubes were available, to-day there are several varieties to choose from, while even the original basic principles of *x*-ray intensification have not remained unchallenged, and there are now two completely different systems.

Principles of Image Intensification

In non-technical language, a bright visual image can easily be produced on any standard fluorescent screen by the use of a high *x*-ray output. Unfortunately such *x*-ray dosage can be utilized for very short periods only, and this has always been the limiting factor in fluoroscopy. *X*-ray intensification is well on the way to solving this problem, by using electronic devices to amplify weak signals which in themselves would not be strong enough to produce a visual image on a fluorescent screen. In other words, more visual light is obtained with a smaller *x*-ray dosage.

Although the electronic equipment is extremely complex and ingenious, the basic principles of intensification are simple. In place of a normal fluorescent screen which converts *x* rays into visual light, the intensifier tube converts the *x*-ray signals via light into electrons which are accelerated and focused down in the tube to produce an extremely bright visual image of reduced size on a small screen at the other end. This bright image can then be viewed through a suitable optical system or photographed with a cine camera. By replacing the cine camera or optical viewer with a suitable television camera, the resultant image can be seen on a monitoring screen, either alongside the *x*-ray table or away in another part of the building. This application of television has at last overcome the difficulties of viewing in ordinary room-lighting by an unlimited number of persons, and the value of this for teaching purposes cannot be overemphasized. It also means that the surgeon can see what he is doing and still remain surgically sterile, thus greatly simplifying the various operative procedures which *x*-ray intensification has made possible.

Recent Advances

The development of television for fluoroscopy has proceeded on two distinct lines. In the older systems an image-intensifier tube provides the light gain, and a vidicon camera is then used to scan the output phosphor and thereby produces a visual image on an orthodox television monitor. The most recent development in this field utilizes a completely different principle which dispenses with the intensifier tube.

The Orthicon Television Camera

The necessary light gain in this system is obtained by the use of a very sensitive orthicon television camera, which scans a modified conventional fluoroscopic screen, the final visual image being produced on a special high-definition 1,024-line television monitor. Provided a minimal light signal is received by the orthicon camera,

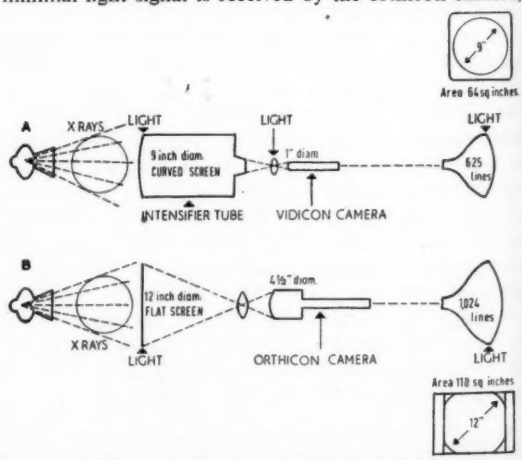

FIG. 1.—A, Image Intensifier System. An intensifier tube produces a very bright visual image on a small fluorescent phosphor. This image is recorded by a conventional vidicon television camera and subsequently reproduced on a television monitor. B, Marconi Orthicon System. The intensifier tube is omitted, but the light-gain is obtained by the use of a highly sensitive orthicon camera which photographs a modified conventional fluorescent *x*-ray screen. The subsequent picture is shown on a special 1,024-line monitor tube which gives much-improved definition.

the brightness and contrast of the monitor can be controlled entirely by manual adjustment in the same way as a domestic television receiver.

The basic differences between the two systems are shown in Fig. 1. It will be appreciated that the vidicon camera is essentially an industrial product, whereas the orthicon is a precision instrument of very high grade developed for the difficult conditions of outside broadcasting. For this particular work the orthicon camera has been modified from the standard television type by incorporating a wider target to mesh-spacing in order to achieve a greater sensitivity. The orthicon camera is more complex and therefore more expensive than the vidicon, and one obviously needs to find good reasons for using this and discarding the great light gain already obtainable with the image intensifier tube.

The main advantages of the orthicon camera system are: (1) the greatly increased definition and improved grey scale of the monitor picture due to the greater sensitivity of the orthicon itself, and the adoption of a 1,024-line system; and (2) the increase in size of the field from a circle of 64 sq. in. (413 sq. cm.) (the largest practicable with the intensifier) to a rectangular field of 110 sq. in. (710 sq. cm.). This increase is obviously of less importance in urology than in thoracic or cardiac work.

The apparatus has great versatility. The image can be doubled in size, shown on the monitor as a positive or negative shadow, and if required projected upside down. This inversion of the image is not of great importance in pyelography unless an extreme Trendelenburg position is required, but for femoral arteriography or cardiac catheterization it does allow an approach to either limb from the free side of the table, without having to view or photograph an inverted picture. Finally, by using a camera lens of 25-mm. instead of 15-mm. focal length, the film image can be further magnified by two.

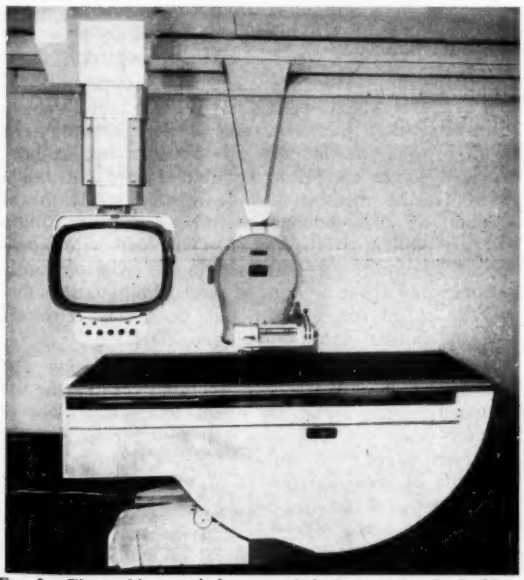

FIG. 2.—The orthicon unit is suspended above a standard tilting table, and can be elevated out of the way when the table is used for conventional radiography. The monitor is also suspended from a ceiling rail and can be rotated, raised, or moved away altogether when not in use.

There are, of course, certain disadvantages of the orthicon, the chief of which is expense, though this may become less of a problem in the future. The set is certainly bulky, but this is to a large extent capable of being counteracted by good engineering (Fig. 2), and the great possibilities of further development would indicate that this is the logical line of progress for the future.

Cinematography

It was originally thought that the necessity of having to film the television monitor before one could obtain a cine record was a major difficulty. However, this has not proved to be the case (Fig. 3). Certainly the cine camera has to be phased to the 50-cycle input main in order to avoid stroboscopic effects, but two of the speeds available (25 and 16⅔ frames per second) are very conveniently close to the standard sound and silent projection speeds, while the ample amount of light and contrast make possible the use of fine-grain 16-mm. film. This can be processed easily in the *x*-ray department and projected within a few hours if necessary, the end results being in every way comparable with those obtained by photographing the phosphor. Certainly a 35-mm. camera is no longer necessary.

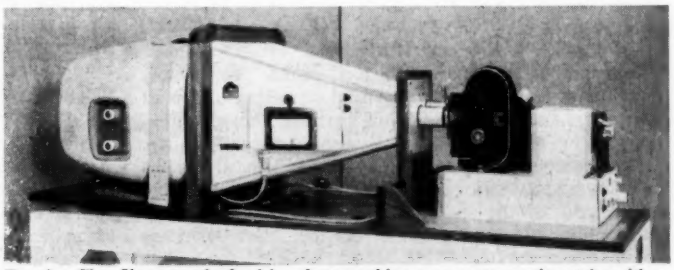

FIG. 3.—Cine films are obtained by photographing a separate monitor tube with a 16-mm. camera, the shutter speeds of which are phased with the 50-cycle A.C. mains. 25 and 16⅔ frames per second are convenient speeds for standard sound and silent projection.

Clinical Applications

The value of *x*-ray fluoroscopy has already been demonstrated in many types of clinical investigation (Hanley, 1957, 1958, 1959a, 1959b, 1960; Stevenson, 1957, 1960), so that the versatility and increased efficiency of the orthicon system will doubtless lead to even further use and development.

Excretion Pyelography

The cumulative *x*-ray dose to the radiologist must prohibit the use of this method for routine excretion pyelograms, but, quite apart from this, our experience shows that the value of intensification is limited because full-size films of first-class quality of the whole tract are essential for preliminary assessment of every patient. This means that the standard I.V.P. examination is still required in the first instance. However, having made this preliminary assessment there are occasions when the use of fluoroscopy is invaluable for studying the dynamics of the tract, using medium excreted by the kidneys rather than medium injected in a retrograde manner. This is particularly so in children or thin adults where good contrast can be obtained using

double-dosage injections. For example, micturating cystograms in children can often be performed without the passage of a catheter, which is obviously desirable when possible, while the normal emptying of the renal pelvis can be studied in the upright position without the presence of a foreign body. This permits differentiation between an atonic pelvis which may be physiologically normal and a truly obstructed or tonic pelviureteric junction which may require surgery.

Nevertheless in spite of the undoubted value of the intensifier for excretion pyelography in certain special instances, its value in routine diagnostic work is limited by the relatively poor density of the contrast medium excreted by the kidney. The newer triiodine molecule compounds have certainly been a great advance on the older substances, but there is still much room for improvement.

Retrograde Pyelography

Retrograde pyelography has been completely revolutionized by the use of visual screening under an intensifier, and we now seldom perform this examination in the old-fashioned way without visual control. The advantages are many. Not only can the dynamics of filling and emptying be studied visually, but the value and quality of the spot films are improved, while the localization of special areas of the tract is made completely accurate.

The ureteric catheter can be passed in the operating theatre or on the *x*-ray table (for preference), and it is only a matter of seconds to visualize the tip of the catheter on the screen and to fill the pelvis under direct vision. The dangers of overfilling and the frustration of underfilling are eliminated and a small spot film is taken at the optimum moment. The whole operation is therefore an exact as opposed to a hit-or-miss procedure. When the spot film has been developed the catheter is withdrawn and, using moderate " foot-down " table tilt, the emptying of the pelvis is watched on the screen. This latter observation proves invaluable time and time again, and among other things has twice revealed the presence of non-opaque ureteric stones and once drew attention to a small ureteric carcinoma which had not been revealed in the excretion or the ordinary retrograde pyelogram. Quite apart from a saving of time and *x*-ray film, the area of body irradiation is much reduced by the coning down of the *x* rays when exposing the small spot film, and this is of great importance.

The quality of the films obtained by this technique is extremely good, while the additional information to be obtained from the visual screening is such as to make one wonder how it was ever possible to do without such facilities.

However, the greatest benefit results from the fact that the maximum information is obtained at the first attempt, for there is nothing less excusable than subjecting a patient to the undoubted risks of retrograde pyelography and then failing to obtain satisfactory radiographs.

Cystography

The technique of cystography has been revolutionized by the introduction of cine-fluoroscopy. Previously a micturating cystogram obtained by a series of still exposures might or might not demonstrate the important phases of filling and emptying of the urethra, or perhaps of ureteric reflux, but a cine film can record the whole cycle of micturition, and can be studied repeatedly and at leisure. Our experiences so far indicate that our knowledge of the basic physiology of the ureter and bladder is only in its infancy.

Other Fields

Gastro-intestinal Examinations.—The equipment is very convenient for the examination of the pharynx and oesophagus where conditions are ideal, with high contrast between the air-filled lung and the barium. When the camera is used, high frame speeds allow projection in relatively slow motion so that the complete cycle of deglutition can be followed in detail down to the stomach. Very minute pharyngeal diverticula can be shown convincingly by this method. In the examination of the stomach, conditions are less favourable for cine-radiography, but it has value in demonstrating rigidity and absence of peristalsis in the stomach wall. Movements of the small bowel are very satisfactorily rendered on cinematograph film and there is throughout the great convenience of screening without prior dark accommodation.

Bronchography and Angiography.—The large field size—110 sq. in (710 sq. cm.)—is of great help when examining the heart and lungs. Selective bronchography can be carried out in excellent lighting conditions and, as in urology, discussion between the radiologist and the clinician during the examination is very helpful. In angiocardiography and cardiac catheterization the screening qualities are quite outstanding, and it is here that inversion of the screen image can be very helpful. The quality of cine-radiography cannot, of course, approach that obtained by full-sized films, and with a single injection of medium, biplane examination is not possible. It may well be that some combination of the two methods will eventually be evolved.

Myelography and Ventriculography.—Here, again, collaboration between surgeon and radiologist is facilitated. Accurate positioning for spot-film technique enhances the value of the examination and reduces the number of films necessary, while it is surprising to find that screening of the lumbosacral area, even in the lateral position, has proved most satisfactory.

Orthopaedics.—Here there is obviously an enormous field available which one has not yet had time to cover. Fracture-setting, joint movement, and arthrography using opaque media are all obvious applications. Provided sterile conditions can be achieved, it would seem that the method may be applied safely to the insertion of intramedullary nails and possibly Smith-Petersen pinning of the femur. The field here would appear so enormous that radiologists will obviously be concerned at the amount of screen examinations that may be called for, as, although dosage is extremely low, one cannot ignore cumulative effects.

Hysterosalpingography. — Fluoroscopy during this examination is now a routine procedure, while the use of magnification technique opens up a new field of research into the effect of relaxant drugs on the Fallopian tubes. In no other investigation is the reduction of radiation dosage of so much importance.

Summary

Our further experience with *x*-ray intensification indicates that some form of television monitoring will become standard practice. The scope of fluoroscopy

has already been greatly increased, while the anticipated difficulties of photographing the television monitor have been overcome.

The Marconi orthicon system, apart from its larger field, would appear to be the most efficient and versatile apparatus at present available, and seems to offer more scope for future development than does the combination of an intensifier tube and a vidicon camera.

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NATIONAL SURVEY OF PERINATAL MORTALITY

FIRST RESULTS

The first results of the National Perinatal Mortality Survey, carried out under the auspices of the National Birthday Trust Fund, were presented at a meeting of the Paediatric Section of the Royal Society of Medicine on April 28. The Survey covered England, Scotland, and Wales.

The director of the Survey, Dr. NEVILLE BUTLER, said that the Survey provided data on perinatal deaths which would have taken an obstetric hospital of average size 250 years to collect; in addition, administrative and clinical data on a control group of one week's national births had been obtained. A large questionary completed one week after delivery or death of the baby, which covered the antenatal period, labour, and details of the infant, was given a successful trial run in Nottingham and Bristol and then launched nationally in March, 1958. Completed questionaries were received on 17,077 births occurring in the week March 3–9 and on 7,932 stillbirths and neonatal deaths taking place in March, April, and May, 1958. These returns represented 98% and 95% respectively of the notified occurrences in England, Scotland, and Wales. In addition, necropsies had been carried out at special centres on 88% of those stillbirths and neonatal deaths occurring in March, 1958. The results now presented were based on a 1 in 3 sample of one week's births and on the March stillbirths and neonatal deaths. Analysis of the full 25,000 cases would be reported later.

Antenatal Care

A review of the antenatal services had revealed interesting features. Twenty per cent. of primiparae and 66% of grand multiparae were booked for domiciliary delivery. But nearly a fifth of these women were admitted later to hospital as emergencies during pregnancy or labour. Cases were analysed according to whether they attended a hospital, local health authority clinic, general practitioner, or midwife. One in three of all women attended a single place of antenatal care, 50% attended two places, and 14% three or more. This multiplicity was of importance, especially as full antenatal notes were reported as not being available in 25% of all deliveries. One-half of mothers attended a hospital antenatal clinic at least once throughout their pregnancy, but this proportion was not greater in cases with a previous neonatal death or toxaemia of pregnancy. First attendance for antenatal care was before the sixteenth week in only 48% of all women, though 70% had attended by the twentieth week. Grand multiparae, unmarried mothers, and women over 40 years all presented later than the average. Hospital bookings were made on the average earlier than domiciliary. Statistics on total attendances during pregnancy, irrespective of quality or spacing, showed that 88% of all woman had attended at least six times, but only 1 in 3 women attended on 12 or more occasions.

As indirect measures of quality of the antenatal services, inquiry was made about rhesus group, haemoglobin test, and chest *x*-ray during pregnancy. The rhesus blood-group was not available in 5% of all deliveries and in 10% of those who received antenatal care completely outside hospital or local health authority clinics. The haemoglobin was not estimated in 32% of all cases and in 60% of those receiving antenatal care solely under the domiciliary service. Chest *x*-ray was performed in 30% of all patients. Finally, 1 in 6 of all mothers reported that their blood-pressure had not been taken on every antenatal visit. It was unlikely that there had been any major change in the standard of care since the date of the survey.

Respiratory Distress Syndromes

Dr. Butler then presented preliminary clinical associations for 100 deaths from hyaline membrane and 52 from massive pulmonary haemorrhage. Males preponderated in each (65%); the incidence of twins was high (22% and 14%). Complications at delivery were commoner preceding hyaline membrane: for example, placenta praevia in 11%, but in pulmonary haemorrhage nil; caesarean section in 27%, but in pulmonary haemorrhage 16%. Complications of pregnancy predominated in pulmonary haemorrhage cases, toxaemia in 65% (25% in hyaline membrane) and "small for dates"—a birth-weight of at least 1,000 grammes less than the average for gestation—in 55% (33% in hyaline membrane), both these differences being significant. Death occurred by 48 hours in 93% of cases of hyaline membrane. The onset of symptoms in pulmonary haemorrhage was usually after the second day, with a maximum mortality on the 3rd–5th day; convulsions occurred in 50% without any intracranial lesion except oedema; haemoptysis (40%) was unaccompanied by other haemorrhages, and vitamin K had been given prophylactically in 45%. Sedation had often been very heavy during labour, and placentae, where examined, were small.

Necropsy Findings

Dr. A. E. CLAIREAUX then gave the results of the March pathology inquiry. Special post-mortem examinations on stillborn foetuses and infants dying within 28 days from birth had been carried out during that month in England, Scotland, and Wales. In each regional hospital board area one or more laboratories agreed to undertake the majority of investigations in that part of the country. Foetal loss and neonatal death could unfortunately seldom be attributed to a single pathological or clinical cause. In order that the clinical and pathological factors could be correlated, the 2,368 perinatal deaths (i.e., stillbirths and first-week deaths) had been classified according to the major lesion found at necropsy. The Table shows the number, percentage incidence, and incidence per 1,000 total births for each lesion in March, 1958. About 10% had more than one major lesion, and these cases were attributed to the lesion considered least compatible with survival.

Signs of anoxia were the most prominent findings among the stillborn foetuses. They were present in 41% of the macerated foetuses, in 57.2% of fresh stillbirths, and in 11% of infants who died within one week. Forty-four per cent. of the macerated foetuses showed no lesion.

Severe congenital malformation accounted for 15.1% perinatal deaths. They were present in 14% of stillborn foetuses and in 18% of first-week deaths. One case in three had multiple lesions. The central nervous, alimentary, and cardiovascular systems were the most frequently affected. Resorption atelectasis, including cases with hyaline

Major Anatomical Findings in 2,368 Perinatal Deaths (Stillbirths and Deaths in the First Week) Occurring in England, Scotland, and Wales During the Month of March, 1958

Necropsy Finding	No. of Cases	Percentage of All Perinatal Deaths	Approx. Incidence per 1,000 Live and Stillbirths
Fresh stillbirth with evidence of intrauterine asphyxia	391	16·5	5·5
Congenital malformation	357	15·1	5·0
Macerated stillbirth without anatomical lesion	347	14·7	4·9
Macerated stillbirth with evidence of intrauterine asphyxia	318	13·4	4·5
Intracranial birth trauma	210	8·9	3·0
Resorption atelectasis with hyaline membrane	138	5·8	2·0
First-week death with evidence of intrauterine asphyxia	101	4·3	1·4
Blood-group incompatibility	95	4·0	1·37
Pneumonia	93	4·1	1·23
Resorption atelectasis without hyaline membrane	78	3·3	1·1
Massive pulmonary haemorrhage	63	2·7	0·9
First-week death without anatomical lesion	65	2·7	0·9
Intraventricular haemorrhage	57	2·4	0·73
Fresh stillbirth without anatomical lesion	17	0·7	0·2
Extrapulmonary infection	7	0·3	0·1
Miscellaneous	29	1·1	0·3
Total	2,368	100	33·13

membrane (5.8%), was present in 9.1% of perinatal deaths. (The relative proportion of all post-mortem lesions in the first week are shown in Fig. 1.) Blood-group incompatibility was responsible for 4% of the perinatal deaths. Birth trauma (8.9%) was rather more frequent than would be nowadays anticipated among hospital confinements. It was probably not unduly high, however, over the country as a whole. It was in this field and that of intrapartum asphyxia that improved obstetric care could most quickly yield better figures for foetal salvage. Infection was surprisingly low. The majority was pulmonary (4%), and extrapulmonary infection accounted for only 0.3% of perinatal deaths. Massive pulmonary haemorrhage accounted for 2.7% of perinatal deaths, and intraventricular haemorrhage (I.V.H.) 2.4%. Infants dying after the first week of life (i.e., 8–28 days) were a relatively small group (163 cases). Congenital abnormalities 42.4%, pneumonia 27%, and extrapulmonary infection 14.1% were the main lesions.

Intrapartum Asphyxia

Dr. M. J. DAWKINS defined intrapartum asphyxia as death caused by asphyxia in labour. The deaths of 451 infants had been analysed for pathological findings and clinical associations: 280 of these were stillborn; 104 were born with a heart-beat but never established respiration; and 67 were born in poor condition and established regular respiration but died within a few hours. Meconium aspiration, visible to the naked eye, was present in a third of all cases.

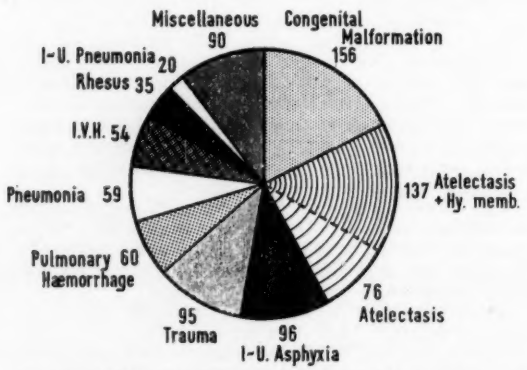


FIG. 1.—Major post-mortem lesions in 901 first-week deaths in England, Scotland, and Wales in March, 1958.

It was not more frequent in the group of neonatal deaths, but its presence could be a serious bar to the establishment of normal respiration. Interstitial emphysema was rare in stillbirths but was present in more than 40% of neonatal deaths. In half the cases of interstitial emphysema a pneumothorax was also present. Endotracheal intubation or mouth-to-mouth breathing had been given in less than half of the cases on pneumothorax. Birth asphyxia by itself could clearly produce emphysema and pneumothorax.

Possible aetiological factors in death from intrapartum asphyxia were classified as mechanical (66%), non-mechanical (60%), and those in which no cause could be found (10%). Overlap was often present. Mechanical factors were mostly associated with labour, and the most important were accidental haemorrhage, placenta praevia, prolapsed cord, long labour, and malpresentations. Non-mechanical factors were a maternal diastolic blood-pressure greater than 90 mm. of mercury and prolongation of pregnancy beyond the 287th day. The incidence of these two factors was significantly commoner in the mothers of babies dying from intrapartum asphyxia than in the control population. They carried an increased foetal risk even in uncomplicated labour, and coexisted in 14% of deaths from asphyxia. Both these factors could reduce placental efficiency. Thus a quarter of the stillbirths were "small for dates" (see definition above) and probably could not withstand easily the asphyxia of normal labour. Grand multiparae and mothers over 35 were also at special risk.

Breech Delivery

Mr. R. G. LAW gave a preliminary analysis of the breech deliveries. Cases of multiple pregnancy, internal version, antepartum foetal death, gross congenital abnormalities, and pre-viable foetuses were excluded. There remained 174 breech deaths to be compared with a control sample of 113 live-born breeches. The incidence of breech at delivery was 2.8%, being 11.9% where the infant was under 5½ lb. (2,500 g.) and 2.1% when over this weight. The perinatal mortality was 10% and was the same in primiparae as in multiparae. In infants under 5½ lb. (2,500 g.) the mortality was 32%. Asphyxia accounted for 70% and trauma 30% of the perinatal deaths. In the smaller infants the proportion of asphyxia to trauma rose steadily as the weight fell. Sixteen per cent. of primiparae and 40% of multiparae went into labour at home, and in all cases the domiciliary mortality was higher, particularly in primiparae with infants over 5½ lb. (2,500 g.), where it was six times the hospital rate.

Although a consultant or registrar was present at a large proportion of primiparous deliveries, the general practitioner or midwife dealt with almost half the multiparous labours. Deliveries by an unsupervised houseman had almost twice the mortality of those by a consultant or registrar. The method of delivery in primiparae was assisted in 67% (80%*), extraction in 17% (2%), and caesarean section in

*Figures in parentheses relate to multiparae only.

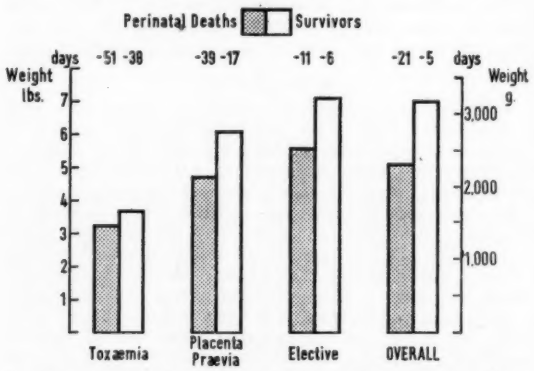


FIG. 2.—Mean birth weight and mean days immature, according to certain indications for caesarean section, in March, 1958.

16% (18%). Breech extractions in primiparae, though few in number, showed an unexpectedly low mortality, 7%, presumably related to the seniority of the operator. In addition to the cases described a small number of breeches were born spontaneously, unassisted, but all of them died.

In the non-premature infants the mortality was inversely related to maternal height, but no special effort had apparently been made to confine the shorter mothers in hospital. Despite the generally accepted importance of pelvimetry before breech delivery, this was done in only one-third of hospital cases; pelvimetry was reported in none of the domiciliary deliveries. The incidence of episiotomy in primiparae was in hospital 96% (79%) and at home 84% (6%). The low incidence in multiparae at home was surprising. The value of forceps in the delivery of the aftercoming head having long been recognized, it was remarkable that in domiciliary deliveries forceps were never used and in hospital they were used in less than one-third of cases.

Mr. Law then gave some tentative conclusions. The higher domiciliary mortality, despite selection of worse risk cases for hospital, argued that the domiciliary delivery of breech presentations should be discouraged. Where a patient had to be confined at home for some exceptional reason, the obstetrician should be able and prepared to arrange for general anaesthesia, perform an episiotomy, bring down extended arms, and apply forceps to the aftercoming head. In deliveries in hospital direct supervision by a consultant or registrar was advisable in all cases, and the high risk with multiparous patients with large babies should be borne in mind. Induction, not later than at 42 weeks, was advised in prolonged pregnancy, and in some cases of premature rupture of the membranes earlier recourse to section was indicated. Considerably greater use of *x*-ray pelvimetry was needed both in primiparae and multiparae, and the value of episiotomy and the application of forceps to the aftercoming head required greater recognition.

Caesarean Section

Mr. D. G. BONHAM then spoke on the preliminary analysis of the caesarean sections in March, 1958. The cases scrutinized were 135 deaths from section in March and 139 control-group sections. The incidence of caesarean section in March was 2.6% of all births, but the caesarean-section stillbirth plus neonatal death rate was 6.8%, compared with 3.4% overall, or 3.12% for the vaginal births. This double mortality in infants born by section was probably related to the cause of the section and justified a study of the indications. Indications for section (figures for survivors in parentheses) were as follows: elective section 25% (12%), toxaemia as main indication 23% (4%), placenta praevia 18% (14%), concealed accidental haemorrhage 7% (nil), other antepartum haemorrhage 4% (1%), foetal distress in labour 11% (16%), delay in labour, including failed induction 7% (21%), disproportion nil (8%), prolapsed cord 3% (3%), malpresentations 4% (4%), diabetes 4% (1%), failed forceps 2% (3%), and ruptured uterus 3% (nil). Attention was drawn to the sixfold difference in the incidence of toxaemia in the lost and surviving infants.

It was possible, by using the March group of lost infants and estimating from the March surviving group, to obtain remarkable mortality figures for caesarean section by indication: disproportion—no losses, delay in labour—2.5%, elective—3.5%, foetal distress and failed forceps both 5%, were all below the mean mortality of 6.8%. Prolapsed cord showed a mortality of 7%, malpresentations 8%, and placenta praevia 9%. The mortality then rose steeply to diabetes and other antepartum haemorrhage at 24%, and the most serious group—toxaemia—at 30%. Ruptured uterus and concealed accidental haemorrhage showed a 100% mortality.

The infants' mean weights and maturity in days prior to the expected date, shown in Fig. 2 according to several important indication groups, illustrated the small mean weight (3 lb. 4 oz.—1,474 g.) and maturity (51 days early) in the toxaemic deaths compared with 3 lb. 11 oz. (1,673 g.) in the toxaemic survivors. Similar figures were shown in the placenta praevia group, although in each case the infants were larger and more mature. Mr. Bonham also drew attention to the maturity of minus 11 days in the elective lost group compared with minus 6 days in the elective survivors.

Of section deaths 5% were macerated stillbirths, 22% fresh stillbirths, 67% first-week deaths (with 37% on first day), and 6% neonatal deaths after the first week. Comparison of section deaths with all infant losses was justified by the very similar weight distribution. Congenital malformations responsible for 12% of section infant losses were similar to the overall 15% mortality. Perinatal deaths from asphyxia were 25% after section and 21% in the total March deaths. In the large group of the neonatal respiratory syndrome an expected but considerable disparity was found. Atelectasis with or without hyaline membrane occurred in 32% of section deaths, but only in 9% of all March deaths. Massive pulmonary haemorrhage at 5% was similar to the total deaths at 3%.

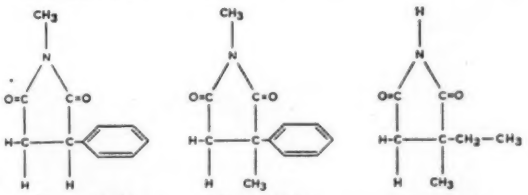
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Ethosuximide

"Emeside" (Laboratories for Applied Biology).
"Zarontin" (Parke, Davis).

Chemistry.—Ethosuximide is α-ethyl, α-methyl succinimide. As shown by the structural formulae below, it is closely related chemically to phensuximide ("milontin") and to methsuximide ("celontin").



Phensuximide Methsuximide Ethosuximide

Pharmacology.—Ethosuximide was synthesized by substituting an ethyl group for a phenyl ring at the alpha position of the basic succinimide molecule and a methyl group for hydrogen in the same alpha position. Compared with the other succinimides, which retain the phenyl group, ethosuximide seems to have gained in efficacy as a method of treating petit-mal epilepsy. The activity of this drug in protecting rats from metrazol-induced convulsions without toxicity has been shown experimentally to be approximately twice that of phensuximide.

Therapy.—Evidence is accumulating to suggest that ethosuximide may be the most effective drug yet discovered for the control of petit-mal epilepsy. In developing new drugs the aim has been to discover remedies with a similar or greater therapeutic effect, but with fewer untoward side-effects, than the oxazolidinediones—troxidone ("tridione"), paramethadione ("paradione"). Phensuximide, though an effective remedy with comparatively few side-effects, has proved to be inferior therapeutically to the oxazolidinediones in many cases, and there is a tendency with this, as with other drugs, for attacks to recur after a satisfactory initial response. The disadvantages of methsuximide are similar. In one recent series[1] of 109 cases treated with ethosuximide, an overall reduction of 85% in the number of attacks was achieved and complete control of attacks for two years was obtained in 42% of patients, with satisfactory control in a further 24%, and partial control in the remaining 26%. In another series[2] of 60 cases, complete and lasting freedom

from attacks was achieved in just over one-third of the cases, a further 20% were improved, and little or no improvement was obtained in 43%. The latter series included several patients who suffered from major seizures or myoclonus or both in addition to petit mal, and in most of them these other epileptic manifestations were also greatly improved. In yet another series[3] of 56 cases, however, it was found that, though petit mal was usually improved, myoclonic and psychomotor attacks were not affected, though they did not appear to be accentuated as sometimes happens in patients treated with phensuximide and troxidone. All authors agree that ethosuximide may safely be combined with other anticonvulsants, including phenobarbitone, the hydantoinates, and the oxazolidinediones. The recommended initial dosage for patients under 6 years of age is one capsule (0.25 g.) daily, and for those over 6 years old two capsules (0.5 g.) daily. The dose can be slowly increased by one capsule a day every 4–7 days up to a maximum of 6–8 capsules (1.5–2.0 g.) daily, depending on individual needs and tolerance.

Side-effects.—The side-effects most often reported have been nausea, gastric irritation, drowsiness, dizziness, and headache, but these have usually been mild and have occurred in under 20% of patients. Skin rashes, transient albuminuria, and temporary neutropenia have also been observed, but no serious blood dyscrasia has been seen in patients treated with this drug. Side-effects often disappear when the dosage is reduced, and do not reappear when it is increased again.

N.H.S. Basic Price.—100 capsules, 250 mg., emeside 27s. 9d., zarontin 25s. 4d.

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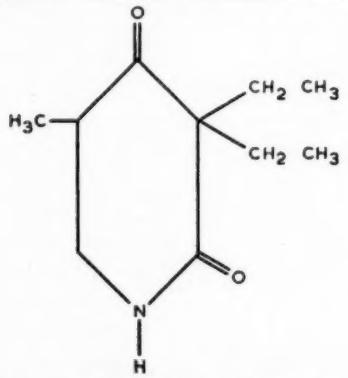
Methyprylone

"Noludar" (Roche).

Chemistry. — Methyprylone is 2,4-dioxo-3,3-diethyl-5-methyl-piperidine. Its structural formula is:



Pharmacology.—The drug has a sedative action on the central nervous system. In therapeutic doses it has no appreciable effect on respiration or circulation, and there appear to be no reports of toxic action on the kidney, liver, or blood-forming system.

Therapy.—Its main use is as a mild, non-barbiturate hypnotic. In doses of 200–400 mg., it induces sleep within half to one hour, and its effects last about six hours. There is evidence that it is well tolerated by the elderly and by patients with chronic alcoholism. It may also be used as a day-time sedative in doses of 50–100 mg., three or four times daily.

Side-effects.—These are uncommon, especially when the dose does not exceed 200 mg. Drowsiness, dizziness, nausea, and headache have been reported.

N.H.S. Basic Price.—50-mg. tablets, 100 for 6s. 4d.; 200-mg. tablets, 100 for 17s. 4d.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Headache and "Eyestrain"

SIR,—In your leading article on chronic headache (April 1, p. 957) you perpetuate the myth that refractive error may be an important cause of frontal headache which can be cured by the provision of spectacles.

I would like to know on what evidence this statement is based. If it is based purely on impression, let me put forward my own impression, which is the result of twenty years' experience. You will recall that the theory usually put forward is that patients with large refractive errors do not make the attempt to correct the error and therefore do not have frontal headache, but that those with small errors make the effort and screw up their periorbital muscles. This in itself seems to be odd; surely the patient with the larger error has the greater incentive for better vision, and should screw up even harder, with bigger and better headaches as a consequence. This is accepted as not being the case. Further, if a careful history is taken, it will be found that the symptom of headache is rarely associated with the minute use of the eyes alone. Over the years I have been advising these people, often young adolescents, to discard their glasses where they do not achieve improvement in vision and where they have been given glasses for headaches which have not improved in any case.

The indications for the use of lenses are simple: they are to improve vision if the patient wants this improvement, and in the treatment of latent and manifest squint. There are no other rational indications.—I am, etc.,

London W.1 H. JACKSON.

Pernicious Anaemia in Jamaica

SIR,—Dr. J. S. Baker (April 8, p. 1038) says it is well known that anorexia, weight loss, and vomiting are uncommon in pernicious anaemia. He is right. It is well known. The error in his argument is that he has assumed that what is well known (that is, generally accepted) is therefore true. That is not so.

Anorexia, weight loss, and various gastro-intestinal symptoms are certainly not rare in pernicious anaemia. They are very common. In classical pernicious anaemia the patient rarely has a good appetite and usually has lost weight. Five years ago my then registrar, Dr. A. E. A. Read, tried to dispel this well-known but erroneous belief with a paper—"Weight Loss and Pernicious Anaemia"[1]—based on the many cases of pernicious anaemia attending my anaemia clinic at the Central Middlesex Hospital. Since then a further paper by Seaton and Goldberg[2] has reported similar findings.

It is important to correct misconceptions, especially when they are widely believed. The belief that weight loss and gastric symptoms are rare in pernicious anaemia is dangerous because it can lead to a mistaken diagnosis of cancer and the risk of death if vitamin B_{12} is not given. That is why I write to point this out.—I am, etc.,

London W.1. RICHARD ASHER.

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2 Seaton, D. A., and Goldberg, A., ibid., 1960, 1, 1002.

Collapse from Reserpine

SIR,—I read with interest your annotation (April 8, p. 1022) on collapse from reserpine, and your suggestion that one should attempt to avert it by stopping the drug two weeks before labour, electroshock therapy, or anaesthesia, so preventing depletion of the body stores of noradrenaline and other catecholamines. I believe the suggestion is, in regard to labour, not merely unwise but potentially catastrophic, because (1) the onset of labour is so variable that one could not accurately time cessation of reserpine (from a graph showing 21 years of obstetrics I found only one baby in ten was born on the expected day); (2) even if accurate timing was possible it would be a mistake at this stage, when the incidence of eclampsia is maximal, to relax control of vasospasm and hypertension in toxaemic patients; (3) in trying to avoid a highly improbable event occurring during labour, it is extremely probable that the severity and danger of toxaemia to the mother and baby would be increased; (4) certain clinical findings[1] are markedly at variance with your statement that repeated administration of reserpine, because of cumulation, greatly reduces the doses required for a given effect. In more than 300 reserpine-treated expectant mothers I have found the initially satisfactory and small dose (0.25 mg. b.d.) has often to be doubled, sometimes trebled, and occasionally quadrupled as term approaches.

For the case of fatal hypotensive collapse during late pregnancy to which you refer, it is reasonable to believe that high dosage, rather than harmful drug, was to blame. With severe toxaemia, or marked hypertension, large doses may be required. Reserpine, however, because of its mild, sustained, slowly developing hypotensive action is far more suitable—almost ideally suited—for dealing with the slow, progressive hypertension of early mild toxaemia. Optimal results can be obtained with minimal danger of untoward effects, if minimal effective doses of reserpine—or of the even milder isomer "decaserpyl" (10-methoxydeserpidine)—are given with a minimum of delay, and continued until term. The need for inconvenient bed-rest can also be minimized.—I am, etc.,

Reading, Berkshire. K. D. SALZMANN.

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Lobeline

SIR,—I should like to comment upon the use of lobeline as a respiratory stimulant in the newborn as discussed in "To-day's Drugs" (February 25, p. 586). Although almost all experimental evidence suggests that lobeline should be of value, the conclusion reached by the expert contributor is the same as that of the authors of many textbooks, namely, that the respiratory response to lobeline in the newborn is "unpredictable and transient." It is not a worth-while respiratory stimulant.

The effects of small doses of lobeline have recently been studied following intravenous injection in the lightly anaesthetized cat and dog.[1] Not only does lobeline act on the chemoreceptors of the carotid sinus to increase respiration but it stimulates other sensory receptors in the pulmonary and coronary vascular beds to depress respiration. The final result in any one animal will depend upon the relative importance and sensitivity of these two effects. In the experiments quoted by Liljestrand[2] marked respiratory stimulation occurred in cats when doses of 300–1,000 μg./kg. were given by *intravenous* injection. At high dose levels the effect of carotid and aorta chemoreceptor stimulation is predominant. However, at low dose levels the responses initiated from the pulmonary and coronary vascular beds are more important. In 50% of the animals studied using doses between 10–20 μg./kg. periods of apnoea lasting 30–60 seconds were observed. Lobeline is given by *intramuscular* injection in doses of 500–1,000 μg./kg. to the newborn infant. As it is fairly rapidly destroyed in the body, the blood level must never be very high. It may be within the range at which stimulation of the sensory endings that lead to respiratory inhibition is likely to be predominant.

If lobeline is to be used as a respiratory stimulant in the newborn infant much larger doses should be employed—but perhaps it were better that it was not used at all.—I am, etc.,

Department of Pharmacology, University of California Medical Center, Los Angeles 24, California, U.S.A. JOHN A. BEVAN.

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[1] Bevan, J. A., and Verity, A. M., *J. Pharmacol.*, 1961, **131**, No. 4. in press.
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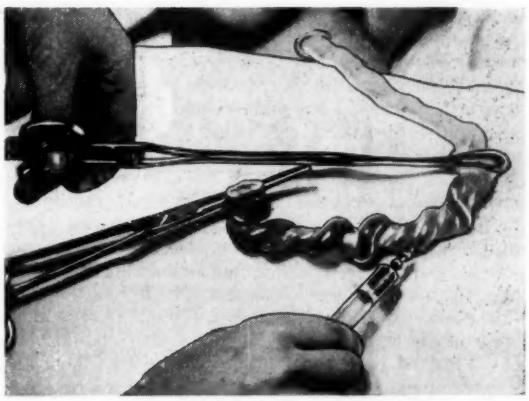
Injection of the Umbilical Cord

SIR,—Soon after delivery the blood within the divided umbilical cord drains into the infant and the umbilical vein becomes almost exsanguinated. This makes the intravenous injection of stimulating drugs difficult if not impossible. There is a grave danger of injection into the umbilical artery, with the risk of skin necrosis over the buttock. The illustration, based on a photograph



taken three minutes after delivery, shows how these difficulties may be overcome. A sponge-holder is placed on the cord 4 in. (10 cm.) from the umbilicus. The cord is then divided between clamps, leaving a 6-in. (15-cm.) length of isolated umbilical vein which remains engorged. Drugs can now be easily injected into the umbilical vein, the sponge-holder removed, and the column of blood containing the drug milked into the infant.

The photograph is reproduced by kind permission of Butterworth & Co. Ltd. from *Illustrated Obstetrics*, which is to be published shortly.

—I am, etc.,

Queen Charlotte's Maternity Hospital, London W.6. J. M. HOLMES.

Dyed Food

SIR,—Your annotation on "Dyed Food" (April 22, p. 1161), one of the most valuable you have published, ends with "Why indeed does our food have to be dyed?" The answer can only be that food should never be dyed, since it is virtually impossible to be sure of the safety of any of the 30 currently "permitted" synthetic coal-tar colours. Thus in 1954 the Food Standards Committee made a list of dyes thought to be safe in food, but a year later decided three of these were not safe, and similar banning of dyes hitherto thought to be safe has occurred recently in the U.S.A., France, and Germany. Further, there is no agreement between the experts of various countries: we ban nine of the 15 colours permitted in the U.S.A., while the U.S.A. bans most of ours. We consider naphthol yellow is safe, but the International Union Against Cancer considers it "unsuitable or potentially dangerous which should not be added to food or drink for man or animals." With such uncertainty about the cancer-causing properties of almost every dye, all should be banned.—I am, etc.,

London W.1. FRANKLIN BICKNELL.

Intravenous "Persantin"

SIR,—My trials of intravenous "persantin," carried out at the request of the manufacturers, have been little more encouraging than those of Dr. D. C. Deuchar (April 1, p. 967) and Dr. H. A. Dewar (April 15, p. 1107) using the oral preparation. As there is impressive pharmacological evidence that the drug is a powerful, though transient, coronary vasodilator, and claims have been made on the Continent that pain may be relieved in patients with coronary thrombosis,[1 2] presumably by an increase in collateral flow at the margin of the infarct, I have studied its immediate effect on the pain of myocardial infarction.

Ten milligrammes of persantin were given intravenously to each of eight patients with severe pain of at least one hour's duration. Four minutes and ten minutes after injection, each patient was asked to classify the effect on the pain as "unchanged, slightly better, much better, or gone." One patient had lost her pain at ten minutes, but no other declared himself anything more than "slightly better." Six more patients were given 20 mg. of the drug under the same conditions. Of these, one lost his pain after four minutes and another after ten minutes, but there was no significant effect in the other four cases. In three of the patients E.C.G.s were done immediately before, and five minutes after, the injection of 20 mg. of persantin, but in no case was there any significant change in the records. Considered purely as an analgesic, intravenous persantin was clearly inferior to such well-tried remedies as morphine and pethidine.—I am, etc.,

Cardiological Department, Bradford A Group Hospitals. P. C. REYNELL.

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Phenazocine and Respiratory Depression

SIR,—Two of your correspondents describe respiratory depressant effects attributed to phenazocine given during anaesthesia; their findings may be correct, but their evidence requires critical evaluation.

Dr. Ronald Shaw (March 18, p. 825) states that the premedication varied and did not "appear to have influenced the results." Since no data are given of the time factor, the slow respiratory rates may, therefore, have coincided with the maximum depressant effect of these drugs, and the evidence is obscured by gallamine triethiodide, by trichloroethylene, and by halothane. (If "shock," whatever that may mean, developed during orthopaedic or varicose-vein operations, it would appear that something was radically wrong.) Dr. A. Vivian Jenkins (April 8, p. 1036) made measurements of tidal volume with a dry gas meter and found "very variable" results. In each of the three patients quoted as examples respiration was depressed before phenazocine was given; therefore we do not know whether the respirations were becoming progressively less at that time.

There may be circumstances when a drug having little respiratory effect on its own may appear to produce severe depression if given at a time when several depressant influences coincide. Patients do not need analgesic drugs during anaesthesia *to relieve pain*; if they can appreciate pain they must be conscious. These drugs may be used during anaesthesia to reduce or abolish reflex activity.

I have found phenazocine of real value in treating patients with severe pain in the immediate post-operative period, provided respirations are not already depressed.—I am, etc.,

Department of Anaesthesia, The University of Leeds. R. P. HARBORD.

SIR,—I have been interested in the letters of Dr. Ronald Shaw (March 18, p. 825) and Dr. A. Vivian Jenkins (April 8, p. 1036) in which are recorded cases of respiratory depression when phenazocine ("narphen") has been used as an adjuvant to anaesthesia.

I have recently been using this drug for this purpose, and now have a series of some 200 cases, of which 81 have been done under controlled conditions similar to those laid down by Swerdlow and Brown[1] in their studies of pethidine and hydroxydihydromorphinone ("numorphan"). My present purpose is to point out that, in spite of their evidence, the strictures of Dr. Shaw and Dr. Jenkins do not, to me, seem to have been borne out in my series. My 81 cases have been operated upon for simple conditions such as hernias, pelvic-floor repairs, mastectomies, etc. Premedication has been light, the majority based on phenothiazine or allied drugs. No relaxants have been given, except in three cases requiring intubation, in which succinylcholine was used. Induction with thiopentone was followed by nitrous oxide, and, in some cases, 1–1.5% halothane, this being usually turned off when the narphen is injected after entering the theatre. Narphen has been given in divided doses of 0.5–1.0 mg. intravenously, the maximum being 3.5 mg. in a radical mastectomy lasting 120 min.

I have been very impressed with the smoothness of the anaesthesia, due to the potency and longevity of action of narphen. This is comparable to numorphan and markedly superior to pethidine, but respiratory depression is less than with either of these drugs. My own recorded series with these is as yet incomplete, but Swerdlow quotes an undue respiratory depression rate of 11% and 8% respectively, with average respiration rates of 13 and 13.5/min. I have noted the lowest respiratory rate in each patient, and the average lowest rate with narphen has been 16.7/min. (range 12–24/min.). Undue depression of respiration has not been

noted, and assisted respiration has been necessary on only four occasions. No case has needed levallorphan, and none has been seen in which conditions have been produced comparable to those described by Dr. Jenkins. Minor difficulties such as movements and coughing have occurred, but have been due to inadequate or incorrect dosage, and have usually been corrected by additional narphen or by halothane. Blood-pressure and pulse rates have been consistently maintained, and nausea and vomiting conspicuously absent, with rapid recovery of consciousness.

An interesting further small series has been undertaken in the ophthalmic theatre, where nine patients undergoing intraocular operations have been given narphen either alone (five cases) or with small doses of thiopentone, a retrobulbar block being effected with 1% lignocaine. Respiratory depression has been no problem in these cases, even in a corneal graft taking 45 minutes and requiring 3 mg. narphen in this relatively short time.

It is hoped later to produce a fuller report on these cases. I feel more work is required on this drug, which seems to have most useful properties, with a minimum of undesirable effects.—I am, etc.,

Royal Berkshire Hospital, Reading. K. BRYN THOMAS.

REFERENCE

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Neuromuscular Block with Streptomycin

SIR,—I read with great interest the article of Dr. G. C. Fisk (February 25, p. 556) on respiratory paralysis after streptomycin and also the memorandum by Dr. Gordon H. Bush (p. 557) of neuromuscular block due to streptomycin.

During March of 1960 I gave an anaesthetic to a patient who had an acute appendicitis with a generalized peritonitis. I ran the patient on intermittent doses of "anectine" (suxamethonium chloride), and during half of the operation I was able to assist his respirations. Just before closure of the peritoneum the patient was breathing reasonably well on his own, though it was entirely diaphragmatic, and at this point the surgeon instilled 4 g. of streptomycin powder into the peritoneal cavity and then prepared to close. I gave the patient 40 mg. of suxamethonium chloride to relax the abdominal musculature so that closure could be facilitated. The wound was closed and there were no signs of the patient making any effort whatsoever to breathe of his own accord. One ml. of "tensilon" (edrophonium chloride) was given with no effect. Artificial ventilation was continued for three-quarters of an hour, when the patient began to make very weak diaphragmatic efforts to breathe. Edrophonium chloride was again repeated with some improvement in the volume of respirations. Atropine 1/75 gr. (0.86 mg.) was administered followed by 2 mg. of "prostigmin" (neostigmine bromide) in divided doses. The breathing improved, but the patient's respirations were still too shallow and weak to return him to the recovery room. A further 2 mg. of neostigmine bromide was given in divided dose without any improvement whatsoever. The patient was then put on to a Jefferson ventilator and his respirations were assisted. After two and a half hours from the end of the operation his general condition and the tone in his jaw muscles had returned and he was now awake. The patient was then returned to the ward, where no relapse into the state of respiratory insufficiency ensued.

About the same time a colleague of mine who was working with the same surgeon had a case of acute appendicitis with peritonitis, and streptomycin in the same dosage was instilled in the peritoneal cavity with the same results as I have mentioned above.

In these two cases the dosage of streptomycin was small—that is, 4 g.—and the surgeon was surprised when informed at a later date of the prolonged apnoea encountered in his patients. He stated he had frequently instilled that quantity into the peritoneal cavity and as far as he was aware no ill effects ensued. However, it would appear that the common denominator was the acute peritonitis with the inflamed peritoneum. The streptomycin was absorbed more rapidly, and hence a much higher concentration would have been available in the blood than, presumably, in those cases in which no such acute peritonitis existed, and hence he had never run into this neuromuscular block before.—I am, etc.,

Bedford, Nova Scotia, Canada. P. E. A. BLAKE-KNOX.

Betamethasone

SIR,—In a recent communication (March 25, p. 876) Drs. J. H. Glyn and D. B. Fox record their experience of a new steroid, betamethasone (16β-methyl 9α-fluoroprednisolone), marketed under the name of "betnelan" (Glaxo). In their cautious appraisal of a pilot trial they conclude that this steroid is of value and deserves further study. Apart from the value of steroids in the treatment of rheumatoid arthritis, these drugs are, of course, particularly useful in dermatological conditions.

It is perhaps worth while, therefore, reporting the results of a similar pilot trial with betamethasone in the treatment of a variety of dermatological conditions. In recent years several new steroids have been introduced, and, understandably enough, one has now come to expect marginal rather than fundamental improvements. In some instances, too, compounds that have promised well have been shown subsequently to possess undesirable side-effects of a special character. This is especially true when very high initial and prolonged maintenance doses may need to be given in certain severe skin conditions such as pemphigus and exfoliative dermatitis. The hope of eventually finding a preparation that has a lower incidence of side-effects is, I think, sufficient reason for examining new drugs of this type.

Thirty patients have been treated with betamethasone. Only cases stabilized on a maintenance dose of steroid for a chronic condition are included in this group. In eight it was possible to make a direct comparison with dexamethasone. This had been given in a dose of 0.5 mg. to 1.5 mg. daily as maintenance therapy for more than six weeks in six patients with alopecia totalis (as an experimental rather than a routine treatment). These patients were able to estimate very accurately the minimum dose necessary to sustain hair-growth. In three of these betamethasone was slightly more effective than the same dose of dexamethasone; in one it was equivalent, and in two no growth occurred with either. The drug was continued for a minimum of three weeks. In another patient with severe atopic dermatitis betamethasone provided slightly better control on the same dose, and in a patient on maintenance therapy for exfoliative dermatitis the same control was achieved.

In 11 patients a similar comparison was made with other steroids by a tablet-for-tablet substitution. Betamethasone appeared to be more effective than prednisolone in two patients with seborrhoeic dermatitis, of equal effect in three patients with extensive eczema or exfoliative dermatitis, and less effective in one patient with a rheumatoid leg ulcer. 0.5 mg. betamethasone was equivalent to 4 mg. methyl prednisolone in two patients with pemphigoid eczema, and less effective in one patient with chronic eczema who developed boils. It was less effective than triamcinolone in one patient with pityriasis rubra pilaris and in one with extensive psoriasis. In all the above patients betamethasone was continued for a minimum of two weeks unless rapid deterioration occurred.

Finally, this steroid was given from the beginning of treatment in 11 patients, over a period of two to eight weeks in doses of 1 to 3 mg. daily. Three patients suffered from severe forms of eczema, two from seborrhoeic dermatitis, two from contact dermatitis, and one each from severe erythema multiforme, exfoliative dermatitis, pemphigoid, and Behçet's syndrome. The last three are on long-term treatment. The response was of the same order as that expected from an equivalent tablet-for-tablet dose of prednisolone. No patient has had to discontinue the drug.

Side-effects observed included moon-face, which occurred in six out of 11 patients who received only betamethasone, and remained in those who had developed this effect while receiving other steroids. This effect appeared to be more pronounced than with prednisolone and usually occurred when the dose was 1.5 mg. a day or more. Undue weight gain occurred in two instances, but in three other patients some of the weight gained on other steroids was lost. Dyspepsia was encountered twice, both times in a mild form and only transiently with a dose of 3 mg. a day. In another patient betamethasone was the only one of four steroids she could take without suffering dyspepsia, and she remains on it without further trouble. Two patients developed boils.

The results of the administration of betamethasone in 30 patients with severe or chronic skin disorders suggest that 0.5 mg. betamethasone is slightly more effective than 0.5 mg. dexamethasone and equivalent to, or marginally better than, 5 mg. prednisolone in 14 patients in which these were compared. Weight gain was less marked than with dexamethasone but more than with prednisolone. Moon-face developed in half the patients treated. Dyspepsia was infrequent.

A study of electrolyte changes and long-term effects is in progress. The length of treatment so far has been short, and a valid assessment of a new steroid must be based on experience over a very long period. Initial results are liable to be over-optimistic. However, this preliminary experience suggests that further trials are worth while and that betamethasone may have some value when side-effects (especially dyspepsia) are encountered in prolonged steroid treatment.

I am grateful to Glaxo Laboratories Ltd. for supplies of "betnelan" used in this trial.

—I am, etc.,

London W.1. D. S. WILKINSON.

Cysticercosis

SIR,—I am particularly interested in the last sentence of your annotation (March 18, p. 804) in which, contrary to generally accepted teaching, it is stated that "it is also important to remember that human cysticercosis is not caused by eating measly pork, but by the ingestion of tapeworm ova. . . ." In Jameson and Parkinson[1] it is clearly stated that "man is infected by eating such meat"—that is, measly pork—and Cameron[2] suggests that "the frequency of cysticercosis in man depends on whether or not meat products are habitually eaten uncooked or slightly cooked."

If cysticercosis cannot be caused by eating measly pork it would appear that the painstaking and time-consuming inspections carried out in slaughterhouses by conscientious meat inspectors are unnecessary. Clarification of this point would therefore be appreciated because of its clinical and practical value on present procedures.—I am, etc.,

Holt, Norfolk. W. H. CRICHTON.

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[1] Jameson, W. W., and Parkinson, G. S., *A Synopsis of Hygiene*, 10th edition, 1952, p. 232, edited by L. Roberts and K. M. Shaw. Churchill, London.

[2] Cameron, T. W. M., *Brit. med. J.*, 1934, **1**, 1110.

SIR,—We agree with Dr. B. Banerjee's comment in his letter (April 8, p. 1039). Man develops cysticercosis through ingestion of the ova of *Taenia solium*. These may come (*a*) directly or indirectly from a worm harboured by another human being, or (*b*) from a worm in his own intestine through contamination of his own hands (possibly long after he was infested) or through regurgitation into his stomach by retroperistalsis. That auto-infection from an individual's own worm—which must have originated through eating infected pork—is not unimportant is suggested by the high incidence of intestinal taeniasis among the subjects of cysticercosis whose histories were reviewed in our recent report.[1] It is true that measly pork is not nowadays likely to be consumed in this country, but we feel that the general statement in the closing remark of the annotation on cysticercosis (March 18, p. 804), "It is also important to remember that human cysticercosis is not caused by eating measly pork," may create a wrong impression.—We are, etc.,

London W.8. H. B. F. DIXON.
Farnham, Surrey. F. M. LIPSCOMB.

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Complications of Chicken-pox

SIR,—We have read Dr. Chava E. Rotem's paper (April 1, p. 944) on complications of chicken-pox with interest, and would like to record a further case of pulmonary embolism occurring in association with this infection which has recently come under our care.

The patient, a man of 37 years of age, developed chicken-pox on February 25, 1961. Two weeks later, on March 10, he complained of pain in his calf, followed by stabbing pains in his chest, breathlessness, and haemoptysis. On admission he was very breathless and in congestive cardiac failure. A pleural rub was heard on the right side of the chest. There was a marked right-ventricular heave with gallop rhythm and fixed splitting of the second heart sound in the pulmonary area. E.C.G. showed changes of acute right ventricular strain and a chest *x*-ray demonstrated bilateral opacities in the lung fields, compatible with infarction.

He was treated with anticoagulants and gradually improved. His cardiac failure, as well as his gallop rhythm, disappeared, and although the pulmonary second sound remained accentuated the splitting became more marked on deep inspiration. *X*-ray of the chest showed clearing of the lung fields. Symptomatically he appears well five weeks after the onset.

—We are, etc.,

P. N. JHA.
K. M. MACKENZIE.
West Suffolk General Hospital, Bury St. Edmunds.

Croup

SIR,—Dr. J. A. Forbes (February 11, p. 389) and Dr. Constance C. M. Howie (March 4, p. 671) discuss tracheotomy in infancy and childhood for laryngo-tracheo-bronchitis. In this connexion I would like to mention the following:

In the winter of 1960–1, when on ambulant first-aid service, I started to treat croup (laryngitis acuta) by elevation. The rapid and certain improvement by this treatment was astonishing. The treatment consisted of holding the child in one's arms, keeping it upright for 15–30 minutes. In the course of this period stridor ceased completely in the ten patients treated by me.

When called by parents over the telephone from their home, and asked to visit the patient, I would often hear the child's stridor through the telephone from the neighbouring room. The parents were then told to carry the child in their arms until the doctor arrived. On my arrival after about 10 minutes, stridor was so modest that in three cases the parents apologized for calling a doctor for no apparent reason. When respiration again became normal, the child was put back to bed in an elevated position, either by lifting the front wheels of the perambulator or by placing the head of the bed on wooden blocks, or by supporting the child with blankets and pillows into a sitting position, but not so high that the child would fall out when he went to sleep. After thus instructing the parents I returned home and asked to be called if anything happened. In the ten cases where I was consulted I heard no more from the parents. On this basis I presume that the effect also of the after-treatment was satisfactory.

Considering that croup sets in after the child has stayed in bed for some time (in a horizontal position) and that oedema of a catarrhal mucous membrane probably is the most important pathogenetic factor, it seems natural to try what may be achieved by elevation treatment.—I am, etc.,

Bekkestua, Norway. TORGILS AANELAND.

Nitrous Oxide in Dentistry

SIR,—Dr. Gaisford G. Harrison has discussed in these columns (March 11, p. 746) his experiences with dental anaesthesia in the upright position. In the introduction of his letter he states that both his patients were anaesthetized with nitrous oxide and 10% oxygen. I thought that anaesthesia by hypoxia was no longer practised. There are so many agents now available which in minimum doses will reinforce nitrous oxide to the point where it becomes an effective anaesthetic agent without having recourse to hypoxia, that the technique used by Dr. Harrison is no longer acceptable. This matter requires emphasis since your journal is widely read by physicians who are not specialist anaesthetists.—I am, etc.,

Department of Anaesthesia, University of Saskatchewan, Saskatoon, Canada. GORDON M. WYANT.

Longevity of Haemophiliacs

SIR,—Dr. A. F. H. Britten (April 1, p. 966) raises for consideration some interesting points regarding the above subject. May I be allowed to mention the following relevant information?

Classification.—As suggested in my letter (March 18, p. 824), I have previously proposed the division of haemophilic and Christmas-disease patients into two groups, with and without *spontaneous* bleeding episodes.[1] These can be identified by a simple laboratory method which consists of incubating at 37° C. the patient's $Al(OH)_3$-treated *undiluted* plasma with equal volumes of patient's serum (1:10), platelet suspension, imidazole buffer *p*H 7.3, and 0.05 M $CaCl_2$. After six minutes 0.1 ml. of this mixture together with 0.1 ml. 0.025 M $CaCl_2$ is added to 0.1 ml. of the *patient's* citrate plasma (substrate). If the clotting-time of the latter is over 60 seconds the patient is considered to be susceptible to spontaneous haemorrhages. All mild cases who suffer no spontaneous bleeding episodes give a substrate clotting-time under 60 seconds, but never below 18 seconds. Normal persons, on the other hand, give 9–10 seconds. The advantages of this system of classification are: (*a*) The method is applicable to both haemophilia and Christmas disease. (*b*) It avoids the measuring of antihaemophilic globulin in *haemophilic* plasma which owing to the presence of Bridge anticoagulant[1] is, in my opinion, impossible to achieve accurately. (*c*) It gives a clear distinction between the normal person with low level of antihaemophilic globulin and "mild" and "severe" haemophiliacs. (*d*) Using this method, the future behaviour of young patients can be predicted without awaiting clinical observations.

Prediction of Operative Bleeding.—By testing the activity of the formed plasma thromboplastin on the patient's substrate rather than on a normal reagent, the conditions existing in the patient's circulating blood are more closely approached. Hence, the usefulness of the above method in predicting and controlling operative bleeding.[2] In order to obtain minimal operative bleeding one should aim at giving sufficient therapy to lower the clotting-time of the substrate to a level well below 20 seconds.

Insurance Risk.—I personally know of at least five cases of haemophilic patients who possess life insurance policies, the insurance companies concerned having full knowledge of their condition. Another patient (Case 6; Nour-Eldin and Wilkinson[3]) was actually covered against unemployment which might arise as a result of accidents in his capacity as a grocer. For life insurance, I have thought and advised that an increase of up to 10% and 20% in premiums for patients with substrate clotting-times below and above 60 seconds, respectively, should be regarded as being reasonable.—I am, etc.,

Blood Transfusion Centre, Brentwood, Essex. F. NOUR-ELDIN.

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1 Nour-Eldin, F., and Wilkinson, J. F., *Brit. J. Haemat.*, 1958, 4, 38.

2 Lambert, V., Nour-Eldin, F., and Wilkinson, J. F., *J. Laryng.*, 1960, 74, 431.

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Prevention of Dental Caries

SIR,—Dr. R. A. Holman's letter (April 15, p. 1110) contains some interesting speculations on the enzymic systems of the cancer cell. From the time when Warburg announced his hypothesis of anaerobic glycolysis, this branch of fundamental research into the cause of malignancy has been of great importance. However, we must not overlook the contributions of empirical and epidemiological research. This is often in a position to confirm or refute laboratory evidence. If Dr. Holman's suggestion is correct that fluoride has a catalase-inhibiting effect *in vivo*, and therefore increases the cancer-inducing potential, then we could expect a significantly increased incidence of cancer in areas where the fluoride content of the water is high. This is not confirmed by studies in the U.S.A., Denmark, and Britain.

The findings of Hagan, Pasternack, and Scholz[1] showed that the mortality rate of cancer per 100,000 of the population was 135.4 in U.S. cities using water supplies containing a fluoride concentration of more than 0.7 parts per million and was 139.1 in cities where the fluoride content was 0.25 p.p.m. or less. Statistics elsewhere show similar results. Even more impressive were the findings of Roholm[2] and the Medical Research

Council's *Memorandum No. 22*.[3] Roholm stated that among Danish cryolite workers inhaling fluoride-bearing dust, who were estimated to be absorbing about 15 mg. of fluoride per day, gastric symptoms and increased density of bone and abnormal calcification were observed, after an exposure to cryolite dust of from 9 to 21 years. On the other hand, Roholm stated: "There is nothing to show that workers acquired microscopically recognizable organic lesions apart from the bone changes." Similarly, the M.R.C. *Memorandum*, referring to workers in two aluminium factories, mentions the absence of disabling symptoms apart from cough and digestive upset, and this was in the case of workers with an average urinary excretion of 9 mg. of fluoride daily.

Dr. Holman himself admits that there is not any good positive evidence (as yet) linking fluoridation with known cancer cases. The work I have quoted above would justify a refutation that there is any association between the consumption of water containing fluoride and the occurrence of cancer. The fact that no such association has been found even when large toxic doses are consumed, taken in conjunction with the fact that the concentration of fluoride for the prevention of dental caries is only 1 p.p.m., should afford further reassurance if any is needed.—I am, etc.,

London W.C.1. A. J. DALZELL-WARD,
Medical Director,
The Central Council for Health Education.

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2 Roholm, K., *Fluorine Intoxication*, 1937. H. K. Lewis, London.
3 Agate, J. N., *et al.*, *M.R.C. Memorandum No. 22: Industrial Fluorosis*, 1949. H.M.S.O., London.

Strontium-90 in Bone

SIR,—Recent research shows that "the ratio of strontium to calcium in new bone of the 1-year-old infant is half that in its current diet, compared with one-fourth in the adult."[1] The Agricultural Research Council's third report gives the highest level of strontium-90 in United Kingdom diets as 80 strontium-90 units ($\mu\mu$c. per gramme calcium). Milk from Merionethshire, Ross and Cromarty, and Cumberland has reached levels of 75.1, 78.4, and 129 strontium units.[2] The highest figure from Cumberland in the latest Agricultural Research Council's report[3] is 73.1 strontium-90 units in June, 1960. Half these figures gives levels of strontium-90 in new bone above the 33.5 "warning level" over the whole population, recommended by the Medical Research Council.[4]

In over 700 examinations of bone strontium-90 in the United Kingdom made by the Atomic Energy Authority, only 38 examinations are from wet, more highly contaminated hill areas. Of these, only three were from children between the ages of 1 and 5 years, when new bone is most rapidly laid down.[5] Thus there is no evidence of the highest levels of strontium-90 actually reached in the more contaminated hill areas of Britain. Many reassurances about their hazards have been given. No extensive investigations of strontium-90 have been made in children of rice-eating, wet, tropical countries. People living on a plant-type diet (rice) have five to six times the level of strontium-90 as those on a milk-type diet (as in Britain).[6]

Thus it is a reasonable conclusion that the levels of strontium-90 in individual children in the United Kingdom and in whole populations of wet, rice-eating Asian and African countries may have now exceeded the Medical Research Council's new "warning level." Hence the concern of the leaders of Asia and Africa.

Is there not an urgent need for the Medical Research Council to investigate actual levels of strontium-90 in children of wet areas of Britain and the Commonwealth, and to set up a special unit to study possible increases of cancer and leukaemia there?—I am, etc.,

Cricket Malherbie,
Ilminster, Somerset. GEOFFREY TAYLOR

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4 Medical Research Council, *The Hazards to Man of Nuclear and Allied Radiations*, Cmnd. 1225, 1960. H.M.S.O., London.
5 U.K. A.E.R.E. reports on strontium-90 in human bone. (Obtainable from H.M.S.O., London.)
6 *A Report to the Medical Research Council by their Committee on Hazards to Man of Nuclear and Allied Radiations on "The Report of the Scientific Committee on the Effects of Atomic Radiation to the Thirteenth General Assembly of the United Nations,"* 1958. H.M.S.O., London.

Mortality from Chloramphenicol

SIR,—Your leading article concerning mortality from chloramphenicol (April 8, p. 1019) did not mention the fairly widespread use of chloramphenicol by dental surgeons as part of root-canal therapy. When this drug is used, a very small quantity (much less than the smallest dose mentioned in your article) is placed in the root canal of a non-vital tooth in an attempt to sterilize the root canal before a root filling is inserted. It is very probable that a minute amount of chloramphenicol finds its way into the periapical tissues and thus into the bloodstream. Is it not possible that this very small dose—perhaps to be repeated during the course of treatment—can sensitize the patient's bone marrow so that future chloramphenicol treatment for some other infection may result in marrow aplasia?

So far as I am aware the problem has not been investigated, and might well be worthy of some consideration in the future.—I am, etc.,

Turner Dental School,
University of Manchester. D. H. CARTLEDGE.

Pancreatic Lithiasis

SIR,—I was most interested in Mr. R. Mahadevan's article on pancreatic lithiasis (March 4, p. 626). I note that diversion of the biliary flow by cholecystojejunostomy or choledochojejunostomy has caused disappearance of the calculi. I would like to know whether an adequately performed sphincterotomy would not have produced the same result by prevention of regurgitation of bile into the pancreatic duct. I would also like to know if any studies of pancreatic function (apart from *x*-ray examination) were carried out in these cases before and after operative treatment. If so, was there any improvement of pancreatic function? Such a study would certainly be of value in the evaluation of pancreatic function.—I am, etc.,

Central Hospital,
Kumasi, Ghana. P. RABINDRAN.

Pelvic Abnormalities in Mongols

SIR,—I read with much interest the article on "Pelvic Abnormalities in Mongols" by Drs. Herbert J. Kaufmann and Willy F. Taillard (April 1, p. 948). I carried out an investigation in 1958 on the pelves of a group of mongols at the Rosewood State Hospital, Maryland, U.S.A. The anomalies of the pelvis which

they report are similar to those I found. In a paper I read before the Royal Irish Academy of Medicine, I summarized my results.[1]—I am, etc.,

Delaware State Hospital, Farnhurst, Delaware, U.S.A. MICHAEL ELYAN.

REFERENCE

[1] Elyan, M., *Irish J. med. Sci.*, 1960, p. 460.

Leg Ulcers

SIR,—I was greatly interested in the article on this subject (March 25, p. 871). Drs. A. Girdwood Fergusson and James C. P. Logan have done good service in cataloguing the various local remedies (pastes, antiseptics, and antibiotics) that one uses in any well-organized ulcer clinic and in in-patient treatment, and also in drawing attention to the desirability of daily or weekly tracings of the regressing sizes of ulcers. I think, however, that their paper goes to show that bed-rest cures most ulcers and that it does not very much matter what medicament is applied. What the paper does not stress is that a leg ulcer is the end-result of a diseased leg—it may be the comparatively rare gravitational ulcer, the all-too-common post-phlebitic leg, the traumatic leg, the ischaemic leg, etc. These *leg* conditions must be treated. It is no use comparing the rate of healing of, for example, "brulidine" (dibromopropamidine isethionate) on two ulcers of equal sizes—in different leg conditions.

I agree that the very worst cases have to be hospitalized; but, given adequate, typed, bandaging instructions to a patient, together with typed instructions about the application of the appropriate local remedy (together with a demonstration to the patient at the time his leg is bandaged in out-patients), as good cures can be secured in the out-patients as in the ward. What treatment is adopted in any given cases depends ultimately upon the experience of the man in charge. I personally have never had much success with eusol or triiodothyronine (of which latter I made some trial owing to the courtesy of Messrs. Glaxo). I have had considerable success with "viacutan" (methargen)[1] and more recently with the "terra-cortril" spray (aerosol containing 100 mg. hydrocortisone and 300 mg. oxytetracycline).[2] Above all—in most cases—bandaging must be firm and supportive with an elastic crêpe bandage.

I can only emphasize again that it is vitally important to treat the leg condition with, for example, physiotherapy, sunlight, bed-cages at night, raising the foot of the bed, exercise by the patient to recanalize a thrombosed leg, and equally important to treat the whole patient—for example, his obesity, arthritis, hyperpiesis. It is a great problem, but it is rewarding work, and with each year one's enthusiasm grows.—I am, etc.,

Liverpool Homoeopathic Hospital, Liverpool 1. STUART MCAUSLAND.

REFERENCES

[1] McAusland, S., *Medical Press*, 1951, **226**, 483.
[2] —— *Practitioner*, 1961, **186**, 227.

SIR,—I read with interest Dr. A. Aitken Ross's comments (April 22, p. 1171) on the article written by Dr. A. Girdwood Fergusson and Dr. J. C. P. Logan (March 25, p. 871). However, I feel he has allowed his delightful sense of poetry to carry him away when he is so upset by the sight of the leg-ulcer patient in a hospital bed.

Everyone who treats lower-leg ulcers wishes to keep the patient ambulant. A considerable percentage of these patients can be so treated by supportive-bandage technique, etc. On the other hand, there are many patients — obese, in their sixties, with swollen oedematous legs—who simply cannot tolerate the pain of supportive bandaging. For them adequate drainage of the limb can only be achieved by rest in bed with the foot of the bed elevated. The ulcer will then heal. The local application is of secondary importance.—I am, etc.,

Department of Dermatology, Bradford Royal Infirmary, Yorks. ALLAN BIGHAM.

"Quite Better"

SIR,—I was interested in the review of the book *Good English for Medical Writers* (March 25, p. 880). It was pointed out that various well-known authors showed some faults in English grammar, among them Jane Austen and Dickens. Looking back, towards the end of a long life, I have read most of the writings of these authors, the two mentioned many times. I am grateful for the pleasure they have given me, and have not worried about their grammar or lack of it. The title *Our Mutual Friend*, for instance, is good enough for me, although it may not be grammatically correct.

I have been worried, however, by the use of the word "better" for "well." The word "better" is used by everyone now, in novels, on the B.B.C., etc., for "well." I had a letter of sympathy the other day expressing the hope that I was "quite better." This I presume meant "quite well." It may be asked, Does it matter? Yes, in my experience it is confusing. When asking a patient, "Are you better?", he will answer at once, "No," although his looks belie him. It takes a long time to make him admit that there is some improvement in health. Anyway, I found it did, although it doesn't bother me now. I suggest that if the word "better" is used all the time for "well" then some other word should be invented for "improvement in health."—I am, etc.,

Newbury, Berkshire. ALLAN FINN.

Representative-free Trimester

SIR,—During the period of influenza in February I decided to stop seeing drug firm representatives. For three months now I have been relieved of these frequent interviews, pleasant and helpful at times, but often irritating, time-wasting, and occasionally frankly annoying. I have found myself more interested in new drugs than before, in that I can critically appraise the numerous advertisements in the medical journals without preconceived ideas consequent on representatives' sales talk.

I would strongly recommend to other practitioners a "representative-free" three months. I am sure many would find it as pleasant as I have.—I am, etc.,

Gloucester. G. C. MATHERS.

E.E.G.s of Boxers

SIR,—Dr. J. L. Blonstein (April 22, p. 1174) describes electroencephalographic studies of boxers conducted by the Medical Commission of the Amateur International Boxing Association and the London A.B.A. Medical Branch. Dr. Blonstein states that the only changes observed were physiological and not permanent.

Since a controversial and highly technical problem of this kind clearly calls for fully documented objective reports by detached investigators, it would be useful to know in what medical journal the above studies were published, who the authors were, and what honorary

or other appointments, if any, they held in boxing associations or clubs.—I am, etc.,

London S.E.5. F. B. BYROM.

POINTS FROM LETTERS

Leg Ulcers

Dr. S. H. F. HOWARD (Barton-on-Humber, Lincs) writes: The most important factors responsible for leg ulcers are circulatory defects and trauma; that of bacterial infection is small. The effort to confirm this widely recognized fact by Drs. A. Girdwood Fergusson and James C. P. Logan (March 25, p. 871) is enormous. . . . Recumbency is described as a routine in treating leg ulcers. Apart from making the sufferer dependent on others, it has been shown of recent years to have a definite morbidity. On rare occasions it may have to be employed before an ulcer will heal; usually an occlusive bandage, renewed as infrequently as possible, is all that is necessary.

Dr. W. SIMPSON (London, N.14) writes: With reference to the letter of Dr. A. A. Ross regarding leg ulcers (April 22, p. 1171), he may be interested in my report in *The Practitioner* of March, 1960, p. 371. I have not found any efficacy in eusol or any other local application. My treatment consists essentially in binding the limb firmly from base of toes to just under the knee and leaving the dressing for at least a fortnight. The sole reason for removing the dressing between times is if it hurts the patient. It is liable to do so sooner or later, as the support and pressure of the bandage removes or reduces the underlying oedema, consequently the bandage tends to slip down and constrict the ankle. The bandage is renewed every two to three weeks, and within a matter of weeks or a few months healing is complete. . . . I omitted to mention that the patients are fully ambulant.

Lumps in the Breast

Mr. ALEX WOOD, F.R.C.S. (Melbourne, Australia), writes: Various letters have appeared concerning cystic lumps in the breast, advocating various courses. It seems that the only safe course is to excise the lump, submit it to frozen (and later paraffin) section, and proceed according to the result obtained as soon as possible. One patient I saw had a cystic lump aspirated, only to find it had returned within a few weeks. It was again aspirated but recurred. The lump was then excised locally, routine section revealing that a slightly thickened area in the wall was a carcinoma. The patient subsequently had a radical mastectomy and radiotherapy. Perhaps the most unfortunate aspect of the whole affair was that both the patient's mother and sister had died with carcinoma of the breast, facts known only too well to the patient.

Caeruloplasmin in Wilson's Disease

Dr. J. M. WALSHE (Department of Experimental Medicine, Tennis Court Road, Cambridge) writes: Although most patients with Wilson's disease have very low blood-levels of caeruloplasmin (less than 10 mg./100 ml.), a few cases have been recorded in which the concentration of this protein may approach or even overlap the normal range (25 to 40 mg./100 ml.). To account for the development of the disease in these patients it has been postulated that they have an abnormal caeruloplasmin, but it has not hitherto been possible to demonstrate the abnormality by electrophoretic, immunological, or enzymatic techniques. Recent work in this department, however, points to a difference in behaviour between Wilson's disease caeruloplasmin and caeruloplasmin from both normals and patients with hepatic cirrhosis under certain specific conditions. Unfortunately, owing to the rarity of the disease, it has not been possible to study sufficient cases to draw firm conclusions. I am appealing, therefore, for samples of serum from patients with Wilson's disease in order to complete this investigation. Five ml. of separated serum is enough for the test, and if the serum is posted early in the week (to avoid being delayed over the week-end) it will arrive in satisfactory condition for analysis.

Obituary

S. A. SMITH, M.B., Ch.M., F.R.C.P., F.R.A.C.P.

Dr. S. A. Smith, a founder and a past-president of the Royal Australasian College of Physicians, died in Sydney on February 5. He was 80 years of age.

Stewart Arthur Smith was born at Grafton, New South Wales, the son of a local schoolmaster; his elder brother, the renowned anatomist and anthropologist, the late Sir Grafton Elliot Smith, F.R.S., became professor of anatomy at University College, London. He studied medicine at Sydney University, graduating M.B., Ch.M. in 1903. His first appointment at the Royal Prince Alfred Hospital, Sydney, to which he later gave many years of valuable service, was that of resident medical officer. He was assistant physician from 1910 to 1922, full physician from 1932 to 1938, and ultimately consulting physician. In 1938 he was appointed lecturer in postgraduate medicine and director of the medical unit at Prince Henry Hospital, Sydney, and, in the following year, honorary physician to the hospital.

Dr. Smith undertook many original investigations, and was keenly interested in the development of medical research in Australia, being for many years chairman of the research advisory committee of the Royal Australasian College of Physicians. Perhaps his greatest contribution in this field was his work for the Life Insurance Medical Research Fund of Australia and New Zealand. The fund was established in 1952 by the Life Offices' Association for Australasia to promote and assist scientific and medical research on the diseases of the heart and blood vessels, and makes grants-in-aid to research departments and awards fellowships. He had been chairman of the scientific research advisory committee of the fund since 1953. He was also chairman of the Australian Rheumatism Council from 1949 to 1959. He was elected a Fellow of the Royal College of Physicians of London in 1949.

Dr. Smith played an important part in the establishment of the Royal Australasian College of Physicians, which was founded in 1938. He was a Foundation Fellow, the first honorary treasurer of the College, holding office until 1944, a vice-president from 1944 to 1946, and president from 1946 to 1948. He served continuously on the council of the College from 1938 to 1956. To the British Medical Association he also gave noteworthy service, being president of the New South Wales Branch from 1927 to 1930 and again from 1946 to 1948. He leaves a widow and three daughters.

H. R. BATEMAN, D.S.O., M.R.C.S., L.R.C.P.

Colonel H. R. Bateman, who had a distinguished career in the R.A.M.C., and during the second world war was deputy director of the Ministry of Health's casualty and ambulance services for England and Wales, died at his home at Worthing, Sussex, on April 1. He was 84 years of age.

Herbert Raymond Bateman was born at Sangoor, India, on October 28, 1876, and received his medical training at St. Thomas's Hospital, qualifying M.R.C.S., L.R.C.P. in 1900. In the same year he entered the R.A.M.C. as a lieutenant, and served in Egypt and Malta before the first world war. He held the rank of captain when appointed a member of the Royal Society's Commission on Sleeping Sickness in Uganda, where he served from 1908 to 1910. With Major-General Sir David Bruce, F.R.S., the director of the commission, Colonel A. E. Hamerton, and Colonel F. Percival Mackie, Bateman was part author of the report which appeared in the *Proceedings of the Royal Society*.

Within a fortnight of the outbreak of the first world war in 1914 he was in France with the British Expeditionary Force, by which time he had attained the rank of major.

Twice mentioned in dispatches, he was awarded the D.S.O. in 1915 for services rendered in connexion with operations in the field. He was promoted lieutenant-colonel in 1918 and full colonel in 1930. After the war, and between periods of duty at home, he served in India and Gibraltar, where he was deputy director of medical services. He retired from the Army in 1933, but returned to duty for another year on the outbreak of the second world war in 1939. He then took up the appointment of deputy director of the Ministry of Health's casualty and ambulance services for England and Wales, which he held from 1940 to 1945. He also acted as chairman of medical boards under the Ministry of Pensions. He finally retired to Worthing in 1947. He leaves a widow.

CONSTANCE M. HIRD, M.B., Ch.B., B.Sc.

Dr. Constance M. Hird (*née* Rostron), who formerly practised in Halifax, died on November 4, 1960. She was 53 years of age.

Constance Mary Hird was born on October 4, 1905, and studied medicine at Manchester, where she graduated M.B., Ch.B. in 1932. After two years in Stockport she moved to Halifax, where she married. She retired from full-time work in 1943, but undertook part-time work thereafter, particularly as medical adviser to the Family Planning Association.

Some colleagues write: Dr. Constance Hird joined the Halifax Family Planning Association clinic in 1944, when the work of this Association was not widely acceptable. Through the years she devoted herself to this work in Halifax and in towns near by. When Spenborough and Huddersfield clinics were started Dr. Hird gave much help and encouragement to workers and patients alike and had continued her association with Spenborough up to the time of her death. In the wider sphere of the work she attended conferences in London, and was for a time on the medical subcommittee. Through her desire to further the work of this association she was instrumental in Halifax becoming a training clinic for doctors and nurses. She will be sadly missed by patients and staff. Her gentleness, kindness, and understanding reassured those who came for advice and help. It has been said of her that there shone out of her such transparent goodness, such quiet and gracious humility, such sympathetic kindness—and with these qualities such unmistakable and yet unselfconscious dignity—that she could not help but make a profound impression on all who knew her. It is to people like her that the Family Planning Association owes so much.

ROBERT RAFFLE, M.B., B.S.

Dr. Robert Raffle, who practised for many years in South Shields, died on February 4, aged 75. He was elected a Fellow of the British Medical Association in 1959.

Robert Raffle was born in South Shields on January 31, 1886, and studied medicine at the medical school of Durham University, where he graduated M.B., B.S. in 1909. After resident appointments at the Beckett Hospital, Barnsley, and the Derbyshire Royal Infirmary, he practised in several parts of Northumberland before joining the R.A.M.C. in 1914. He married in 1916 and returned to South Shields four or five years later to set up a practice which was taken over by his son about three years ago.

Dr. JAMES I. SMITH writes: As one of the older general medical practitioners in South Shields I knew Dr. Raffle for well over thirty years and served with him on numerous committees. I was greatly impressed by his integrity and strength of character, and his guidance will be greatly missed both by medical and by lay members. Beneath a rather gruff exterior he was a kindly man who was respected both by his patients and by his fellow general practitioners.

At the time of his death Dr. Raffle was chairman of the executive council in the town, having been a most able chairman for ten years. He was also a member of South Shields local medical committee and had previously been the chairman as well as its representative on the health committee of the local authority since 1948. Dr. Raffle was also a member of the executive committee of the South Shields Division of the B.M.A. from 1929 to 1948 and from 1951 to 1954, and was chairman from 1942 to 1948. He was a representative on the branch council from 1941 to 1948, a member of the ethical committee since 1952, and in addition he had been a member of South Shields district hospital management committee from 1948 to 1954. During the last war I worked with Dr. Raffle on the local medical war committee, on which he did valuable work.

From 1913 Dr. Raffle was an active Freemason. For seven years he was Assistant Provincial Grand Master in County Durham and was a founder member of many lodges and held several ranks in the United Grand Lodge of England.

Dr. Raffle, the only Fellow of the British Medical Association in South Shields, is survived by a son and daughter, who had to bear the sad loss of both parents within a week, for Mrs. Raffle died only six days before her husband. I am sure his many friends, both in the profession and outside, will join with me in offering the family our deepest sympathy.

GEORGE BUCHANAN, M.D., D.P.H.

Dr. George Buchanan, formerly deputy director of the South African Institute for Medical Research, and professor of clinical pathology in the University of the Witwatersrand, died at his home in Johannesburg on February 13 after a long illness. He was 78 years of age.

George Buchanan was born in Edinburgh on July 7, 1882. As a young man he was an assistant in the medical laboratory at Khartum, where he met the late Sir Andrew Balfour, who encouraged him to study medicine at Edinburgh University. A brilliant student, he gained medals in botany, zoology, histology, and pathology, and graduated M.B., Ch.B. in 1918. During the first world war he served first in the Royal Navy as a surgeon-probationer, and then as a temporary captain in the R.A.M.C. in France. While in the Navy he was given special leave to take his final medical examination. He proceeded to the M.D. in 1925, being awarded a gold medal for his thesis on spirochaetal jaundice in Scotland, especially among coal-miners, and in the following year he was awarded the Lister fellowship for original research by the Royal College of Physicians of Edinburgh. He took the D.P.H. of the Scottish Royal Corporations in 1924. After the first world war Buchanan held a number of interesting appointments, including those of curator of the museum of the Wellcome Bureau of Tropical Medicine, assistant pathologist and, later, lecturer in bacteriology at Edinburgh University, and clinical pathologist and tutor at Edinburgh Royal Infirmary. For a period he was a full-time research worker under the Medical Research Council, and in 1927 the Council published his important report on spirochaetal jaundice in Scotland as No. 113 of its Special Report series.

In 1926 Buchanan went to South Africa to assume the newly created appointment of superintendent of the Routine Division of the South African Institute for Medical Research. He occupied this post until 1940, when he was appointed deputy director of the institute. In 1936 he became the first honorary professor of clinical pathology in the University of the Witwatersrand. He retired from the chair in 1949 and from the post of deputy director in 1950, but continued to serve the institute as a senior research officer for a further seven years. He was a member of the Leprosy Board of the Union of South Africa's health department over a long period. His work for his adopted country and

for his profession was rewarded in 1959, when emeritus membership of the South African Medical Association was conferred upon him. He was a skilled painter of landscapes and was keenly interested in medical art. He leaves a widow and two daughters.

E. B. BERENICE HUMPHREYS, M.B., Ch.B.

Dr. E. B. Berenice Humphreys, formerly maternity and child welfare medical officer in Leicester, died in retirement at Wargrave, Berks, on February 12. She was 63 years of age.

Evelyn Bertha Berenice Humphreys graduated M.B., Ch.B. at Edinburgh in 1925, and four years later she came to the City of Leicester health department as the first senior medical officer for maternity and child welfare, continuing in this post until her retirement in January, 1958. Dr. Humphreys possessed immense drive and energy, and the mothers and children of Leicester owe much to her enthusiasm and keenness. She will be remembered beyond Leicester for the excellent home-help service she initiated and for her work with the pre-school deaf child. It was largely due to her enthusiasm that Leicester was the first local authority to provide an audiology clinic and a screening programme for hearing as part of the maternity and child welfare service. In this work she received invaluable help, guidance, and support from the late Lady Ewing. In 1950 she was president of the East Midlands Branch of the Society of Medical Officers of Health.

Dr. Humphreys's death, coming so soon after that of Dr. E. K. Macdonald, her chief for 23 years, closes a chapter in the life of the City of Leicester health department which may never again be emulated for the change, expansion, and advances made in such a span of years.—T. A. I. R.

J. D. GRIERSON, M.B., Ch.B., F.R.C.S., F.R.C.S.Ed.

Mr. J. D. Grierson, who formerly practised as a surgeon in Georgetown, British Guiana, died at Bath on February 23. He was 62 years of age.

John Darbyshire Grierson was born in London, the son of a Presbyterian minister. He was brought up in Plymouth and served with the Argyll and Sutherland Highlanders during the first world war. Graduating M.B., Ch.B. at Edinburgh University in 1920, he became a Fellow of the Royal Colleges of Surgeons of England and of Edinburgh in 1925. Two years later he was appointed surgeon specialist at the Public Hospital, Georgetown, British Guiana, the first holder of this post. He soon had a great personal success and revolutionized surgery in the colony, becoming in a short time very popular with the multiracial inhabitants of British Guiana. To his notable skill was added a cheerful disposition and a keen sense of humour, and he inspired great affection and loyalty in his colleagues at the hospital. He had no time for red tape, and the delays and inefficiency associated with Government procedure often aroused his ire. He retired in 1949 because of ill-health and lived first in Cornwall and then in Bath. He is survived by his widow and three children.

C. W. ELSON, M.R.C.S., L.R.C.P.

Dr. C. W. Elson, who was in general practice at Worthing for nearly thirty years, died suddenly at his home there on March 3. He was 67 years of age.

Cyril William Elson was born on July 20, 1893. He studied medicine at Leeds University, and qualified M.R.C.S., L.R.C.P. in 1920. He then held the appointment of clinical assistant at the Royal Eye and Ear Hospital, Bradford, before entering general practice in Leeds and then in Bradford. He moved to Worthing in 1932, and remained in practice there until the time of his death, which came after his morning round of visits. Kindly and courteous, his chief concern was the welfare of his patients. A member of the British Medical Association for 38 years, he was honorary secretary of the West Sussex Division from 1939 to 1945, and he also gave valued services as joint honorary secretary of the local medical war committee for several years. His interests outside his profession included archaeology and music; he was president of the local archaeological society in 1934, and a member of the committee of the music society for some time. He was also a past-chairman of the Worthing branch of the English Association. He leaves a widow, a daughter, and a son.

M. G. PEZARO, M.B., Ch.B., B.Sc.

Dr. M. G. Pezaro, a well-known general practitioner in Auckland, New Zealand, died there on March 4. He was 64 years of age.

Marcus George Pezaro was born in Melbourne, Australia, on September 9, 1896, but was taken to New Zealand at the age of 7, and received his early education at Auckland Grammar School. He gained a university scholarship in 1913 and again in 1914, when he was dux of the school, before going on to Auckland University College, from which he graduated B.Sc. in 1916. Joining the New Zealand Army, he served overseas with the Signallers for the remainder of the first world war. At the end of hostilities he was granted an Army scholarship and entered Glasgow University as a medical student. After taking the degrees of M.B., Ch.B., with honours in midwifery, in 1922, he held the appointments of house-physician and senior house-surgeon at Gloucester Royal Infirmary. He returned to New Zealand in 1924, and established what was soon to be a very large private practice in Auckland. In addition, he became honorary anaesthetist to Auckland Hospital. Despite ill-health and a developing cataract, he remained at work until a short time before his death.

A member of the British Medical Association for nearly forty years, he was chairman of the Auckland Division in 1942, and from that year until 1960 he was a member of the benevolent fund subcommittee of the Division. His chief interest outside his profession was racing, especially trotting. A member of the committee of the Auckland Trotting Club for twenty-eight years, he was president of the club from 1946 to 1960, and president of the New Zealand Trotting Conference in 1955 and of the Totalizator Agency Board. Ever generous, he was always ready to support a deserving cause, and his loss will be deeply felt by all his old patients. He leaves a widow, two sons, and a daughter.

J. J. McCANN, M.D., LL.D.

Dr. J. J. McCann, who gave up medicine for a political career in Canada and became Revenue Minister in Mr. Mackenzie King's administration in 1945, died in hospital in Ottawa on April 11. He was 74.

James J. McCann was born in Perth, Ontario, and graduated in medicine at Queen's University, Ontario, in 1909. He practised as a physician in Hamilton and Renfrew, Ontario, being also coroner in Renfrew. Elected to the Canadian House of Commons as Member for Renfrew in 1935, he was chairman of the Canadian delegation to the World Health Organization in Geneva in 1950. After serving as Minister of Revenue under Mr. Mackenzie King and Mr. Louis St. Laurent he lost his seat in the 1957 election and retired from politics.

JOSEPH MINTON, F.R.C.S.

The obituary of Mr. Joseph Minton was published in the *Journal* of March 25 (p. 909).

Mr. CLIFFORD MORSON writes: Your obituary of Joseph Minton accurately describes his character and career. I was a member of the medical committee of the Hampstead

General Hospital which appointed him consultant ophthalmic surgeon in 1936. At the time there were misgivings about the choice, but these were rapidly dispelled. He quickly proved to be not only a brilliant eye specialist, but popular with everyone. If the size of an out-patient clinic is an indication of the ability of a consultant, Minton was in the forefront of his specialty. In his hospital work nothing was too much trouble. He handed out his knowledge of eye diseases to all and sundry. He was always teaching in the wards, the operating theatre, and in the out-patient department. All his hospitals will miss him.

J. J. McCANN, M.B., B.S., M.R.C.P.

The obituary of Dr. J. J. McCann was published in the *Journal* of April 8 (p. 1046).

E. F. C. writes: As a general practitioner fortunate enough to live for many years within a mile of Pinewood Hospital, I would also pay my tribute to John McCann. His influence extended beyond the boundaries of his hospital, and we who practised in the surrounding district remember with deep gratitude the help that he gave us. In this respect he continued and developed the tradition established by his predecessor, Dr. Fowler. To take a patient to Pinewood for consultation was always a pleasure and an education. Despite the pressure of his work, John McCann's demeanour was invariably calm, deliberate, unhurried. There seemed no limit to the time and trouble that he was prepared to devote to a case, so that to us outside, struggling with the adverse conditions of general practice, McCann represented perfection, and so became himself the symbol of medicine as it ought to be. In local medical circles he will be greatly missed, and our deep sympathy goes out to his widow and young children.

HAMILTON BAILEY, F.R.C.S., F.A.C.S.

The obituary of Mr. Hamilton Bailey was published in the *Journal* of April 8 (p. 1043).

Dr. ALAN KLASS, of Winnipeg, writes: To students of surgery, undergraduate and postgraduate, in the British Commonwealth and in many other parts of the world the name Hamilton Bailey is a memorable one. I believe that it was by his writing—more than by anyone else—that British surgery became esteemed and renowned throughout the world. In the period between the wars—to my generation of medical students—Bailey's *Demonstrations of Physical Signs in Clinical Diagnosis* and Bailey and Love's *Textbook of Surgery* and Bailey's *Emergency Surgery* were perhaps the best-known examples of British surgical writing. They were lucid, they were well illustrated, and with rare judgment they pointed out what was important in the welter of information a student has to assimilate. The repeated editions of these works is ample evidence of the sustained demand by succeeding generations of students. It has seemed to some of us from the "Dominions" rather curious that in his own country there appeared to be less than full recognition of Hamilton Bailey's importance in the growth of the reputation of British surgery throughout the world: without entering into the subtleties of the origin of honours lists, it has seemed surprising that a name towering across the borders should not have parallel recognition within his own country.

Hamilton Bailey had among his many gifts great charm and friendliness. Not only his clinics but his home was always open to visiting students without regard to race, colour, or creed. Innumerable "colonials" found a warmth and a hospitality so hard for the shy unheralded visitor to find. Veta and Hamilton Bailey's home became a haven for so many of us on subsequent visits to England. There friendships were formed enduring beyond time and space.

Thus in many parts of the world there is a real personal sense of loss in the death of a great man and a close friend. Only Veta can understand this fully, and her we face from many corners of the world in warm and deep sympathy.

Medico-Legal

PARENTAL CONSENT TO TREATMENT

[FROM OUR LEGAL CORRESPONDENT]

If a parent were to expose his naked baby in the snow and forbid approaching strangers to touch the child, could he bring an action for assault (1) on behalf of the child if one took the child to warmth and safety, or (2) on his own behalf if one assaulted him for the purpose of effecting such removal?

Assault

It is an assault even to touch a person without his consent, subject to certain defences. A child without sufficient understanding is incapable of giving consent, so that the power to give or withhold consent is vested in the parent. Yet it is an affront to all human feelings to consider that either action in such circumstances could succeed for even nominal damages. The position is even stronger when a child is entrusted to a hospital, is found to be suffering from a disease which will lead to certain death, and for which there is only one known treatment, and the parents refuse to give consent to that treatment.

Such a situation has arisen when parents have refused, on religious grounds, to give consent to blood transfusion for rhesus-positive babies. On such facts, however, it is difficult to find a recognized defence which will apply to an action for assault. The first to spring to mind is the defence of "necessity," but this is an ill-defined defence and there are no helpful authorities supporting the defence of necessity in cases of assaults to the person. If a defence to such an action exists, it must be supported on general principles.

Furtherance of Breach of Duty

There are two considerations which, it is submitted, are of overriding importance.

First, if the parents of a child in hospital could not be contacted, it would be the duty of the hospital authorities and staff to do all they could to heal the child, notwithstanding the absence of any instructions for or consent to treatment.

Secondly, if a parent fails to provide adequate medical aid for his child, he commits a crime under Section 1 of the Children and Young Persons Act, 1933. The refusal to allow an operation vital to the life of a child must (so long as there is no reasonable doubt about the efficacy of the operation) constitute such failure.

Generally, a doctor is said to be given implied consent or authority to give treatment in the case of a person in his care who is incapable of giving consent (e.g., an insane, unconscious, or very young person).[1] The parents or a guardian of a child, when available, may withdraw that implied consent, and it is to them that the doctor must look for consent on the child's behalf. But that giving or withholding of consent must be exercised according to law, and, if it is exercised in clear breach of legal duties, then, it is submitted, the doctor is under a duty, legal as well as moral, to avoid collaborating in that breach of duty.

Similar principles apply, it is submitted, to the case where a parent is forcibly removed from hospital to prevent him removing his child from the care of the hospital. If the child was in urgent need of an undisputably vital operation the hospital authorities should have a good defence to an action in respect of the assault on the parent so long as only reasonable force was used. It must be stressed, however, that this is only speculation.

Preservation of Life

In this connexion it is interesting to compare the position of a doctor who administers an antidote to a would-be suicide contrary to the expressed wishes of the patient. By a majority of four to two the Court of Appeal of New York has held that this is not trespass,[2] though the point

seems to be undecided in England. Does this decision rest on the consideration that the refusal of consent is made in the furtherance of a crime? Will the position be any different (in the case of a sane person who has attempted suicide) when, and if, suicide is no longer a crime?

A case of a different nature which also makes interesting reading is one of an action in assault[3] brought by Mrs. Marie Leigh, who sued Mr. Gladstone and certain prison officers for having subjected her to forcible feeding while she was on hunger strike in prison. The court held that necessary feeding was justified by the duty imposed on prison officers to preserve the health and lives of prisoners in the custody of the Crown.

REFERENCES

1 Addison, P. H., *Brit. med. J.*, 1960, **1**, 976.
2 *Meyer v. Supreme Lodge K.P.*, 1904, 70 N.E. 111 (N.Y.).
3 *Times Law Reports*, 1909, **26**, 139.

Medical Notes in Parliament

LORDS ON HOSPITAL SERVICE

[FROM OUR PARLIAMENTARY CORRESPONDENT]

The debate on the hospital service in which the House of Lords engaged on April 26 was firmly linked from the start with the address delivered by the Minister of Health to the National Association of Mental Health in March.* This was the speech in which Mr. Enoch Powell forecast that 15 years hence half the existing mental hospital beds would not be required.

Lord STONHAM, opening the debate, put the overriding question of the moment in the hospital world as how to get full value for the money available: on the one hand was the rising demand for medical care; on the other, the Government's decision to reduce the share of the gross national product available for the Health Service. The Minister, he acknowledged, had made a good start seeking the help of the regions to get on paper a picture of the hospital service in the middle nineteen-seventies. That really meant spending for 20 years ahead, instead of five. Subject to two vital considerations it would provide a better service at less cost. These considerations were: (1) that the planning was not forced into some tidy, preconceived, Whitehall notion; and (2) that the Minister realized that it was not glass and chromium that made a good hospital but the quality of the staff, and that he must carry the staff with him in any changes.

Minister's "Disastrous" Speech

In his "disastrous" speech to the Mental Health Association the Minister had ignored both. He had declared that in fifteen years 75,000 (that was half) of our mental hospital beds would not be required, and that by far the greater part of our mental hospitals would be eliminated. He had said that his forecast was based on present trends, but that he wanted to speed up those trends and to pitch the estimate lower still, "as low as we dare, perhaps lower." That was dangerous nonsense. The validity of the Minister's statistical projection was challenged by the fact that it was based on heavy overcrowding; that 78% of patients were long-stay cases, and that these numbers would be increased by greater longevity and an expanding population; and by the fact that 40% of those who went home relieved had to be readmitted.

On general hospitals, he asserted the opinion that, except in newly populated areas, more beds and more hospitals were not needed, in spite of the long waiting-lists. Most hospitals had empty beds, and the beds were under-used. If the average duration of stay were cut by one day the waiting-lists could be wiped out. If the turnover interval between patients was cut by one day it would be the same as providing 15,000 extra beds, which would cost £60m. to house in new hospitals. On the vital question of clinical cleanliness he said that, since every new hospital was obsolescent before its working days started, available money should be spent first on ending the appalling situation in existing hospitals, which meant that the risk of catching a new infection was greater in hospital than at home. It was a very difficult problem; it would take brains, time, and money—and will—to solve; but it would be intolerable if it was not accorded top priority. Yet so far the hospitals had not been given an extra penny with which to fight it.

*See *Brit. med. J.*, March 18, p. 820.

If Schizophrenia Were Controlled

The Earl of FEVERSHAM, chairman of the National Association of Mental Health, contested some of Lord Stonham's strictures on the Minister. Expressing the association's pleasure in finding that the Minister sided with what they regarded as enlightened progress, he said they agreed most emphatically with the principle of abolishing the greater part of the old mental institutions; they agreed with integrating psychiatric units in the general hospital service; and they agreed with the building up of local authority provision for community care. One factor that would affect the role of mental hospitals was the possibility of a break-through in research into schizophrenia in the next 10 years. About one person in every 100 born would suffer from schizophrenia, the largest of all causes of mental disablement. There were nearly 60,000 patients in hospital in England and Wales now. A cure, which might not be far off, would have dramatic implications. About one-third of mental hospital beds could be emptied overnight. He begged the Minister to give further support for research in mental health, which was far from adequate. But he agreed with Lord Stonham that there were nowhere near enough trained workers to staff the inadequate community care services existing, far from being enough to establish new and better services; and he endorsed the suggestions made by Professor Titmuss for a £10m. grant to local authorities for community care services; that Government grants should be provided for all social work students and training courses, irrespective of specialty, at universities and technical colleges; and that there should be a Royal Commission on the recruitment and training of doctors, with special reference to the need for education in social and psychological medicine.

Local Authorities' Obligations

Lord AMULREE urged that local authorities should be encouraged—"or even more"—to fulfil their obligations under the National Assistance Act to provide residential accommodation for the aged and infirm, so that hospital beds could be freed for the sick and disabled.

Lady SUMMERSKILL asked for greater humanity of treatment towards women in childbirth; better pay and conditions in the midwifery service—starting with an independent committee—and action to reduce the suffering associated with long waiting-lists.

Viscount WAVERLEY drew on his experience as a consulting physician to press the claims of auxiliary staffs, of whom he said that the problem of inadequate pay, failure in recruitment, and continuous wastage blighted the whole hospital service. Salaries and conditions must be equated with those of the Scientific Civil Service, and ever-increasing use made of automation for routine tasks. The Earl of LONGFORD, chairman of the National Society for Mentally Handicapped Children, supported the need for a special unit for research in mental deficiency, which did not appear to occupy a very high status in the medical world; and said there was a strong feeling among parents of the mentally handicapped that they should be taken into much closer consultation with hospital committees.

Let Boards Carry Forward Unspent Money

Lord TAYLOR, drawing the threads together in the last speech before the Government reply, gave endorsement in blunt phrases to much that had been said. Hospital boards

should be allowed to carry forward unspent money each year, and thus avoid "the absurd rush to spend money on third-, fourth-, and fifth-rate priority jobs." If they had that liberty they would provide a far better service and a cheaper one. The Whitley Council machinery was "rotten from top to bottom." Many of the things fundamentally wrong with the hospital service stemmed from staffing with people who had no direct negotiating machinery with the Treasury.

Mental hospitals fell roughly into two classes—those with under 1,000 beds, and those with over 2,000. "My experience of those with 2,000 or more is that the only treatment is the bulldozer." Eighty or 100 beds were needed to get a good psychiatric unit inside a big hospital. But it would be a tragedy if, because of the new conception of the acute psychiatric unit, they said the mental hospitals of 800 beds were no good. They were true therapeutic communities. He hoped the Minister would have second thoughts about the extremely sweeping speech he had made suggesting that they were all to go. They would all go one day, but they must not destroy good work that was being done so long as there was a need for it.

Improve Old Hospitals

He complimented the Ministry on its building notes for new hospitals—"sensible guidance"—but insisted that it was more important to bring old hospitals up to standard. "Community care" was a catch phrase. The only way to get it was to base it from the hospitals; it was wishful thinking to say that local authorities could do it. It was depressing to see the Government pinning their faith on community services which did not exist. The off-loading of patients from the hospital into the community was a good thing if it could be done. They wanted to encourage keeping people at home. "But do not ask the general practitioners to do any more. There are too few, and the supply is going down rapidly." This was the result of the Willink Committee's mistake in recommending a 10% cut in the intake into medicine. General practitioners were worked off their feet. They could not do better work until list sizes were reduced. A few large-list men made a great fuss and said they could look after 3,500 properly. "But 99% of general practitioners will tell you that is nonsense, and they are right."

The Platt Report† suffered from one defect common to Government documents: the people who wrote it were almost all teaching hospital staff. Where the Working Party went wrong was that they did not know what life was like in the peripheral hospitals. One thing they had shown was that a quarter of all the junior staff was non-British. Casualty departments were not properly staffed. It took an average of 21 minutes for an ambulance to get a person to hospital in London, but once there they hung about for hours. "A surgical colleague of mine, knowing what would happen to him if he were involved in a car smash, and knowing the varying service available, has suggested tattooing on each limb the appropriate hospital to which he should be taken in the event of that particular organ being injured. And, knowing one's hospitals, that is not a bad idea."

Government Reply

To answer all this for the Government, Lord NEWTON could do little beyond quote various reports, and expand on figures of capital investment growth over the past few years. One of more than a score more of building notes would give interim guidance on casualty and accident departments, and an inquiry into casualty services by a subcommittee of the Central Health Services Council under Sir Harry Platt was examining statistical and written evidence. The Minister's estimate of reduction in mental hospital needs was based not on pious hopes, but on a statistical projection of what happened during 1954–8, and the development of improved methods of treatment. He offered an assurance to the hospital staffs that they need have no anxiety about a reduction in numbers; fewer beds did not mean a reduction in the psychiatric services, and there would be no reduction in the opportunities for special skills. On the Whitley system and the pay of auxiliary staffs, he said they must be realistic. There had been many gratifying increases in numbers over the past 10 years. No one had suggested a better system. The appropriate comparison was to be made with other public services. The hospital service got a reasonable share of the personnel available.

†See *Brit. med. J.*, March 25, p. 883; *Supplement*, p. 99.

Universities and Colleges

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College held on April 13, with Sir Arthur Porritt, President, in the chair, Mr. W. J. Dempster, F.R.C.S.Ed., and Mr. O. D. Morris, F.R.C.S.Ed., were admitted to the Fellowship *ad eundem*.

The death of Dr. Howard C. Naffziger, Honorary Fellow, was recorded with deep regret.

The Jacksonian Prize for 1960 was awarded to Mr. C. R. Helsby, F.R.C.S., and a certificate of Honourable Mention to Mr. H. Hamilton Stewart, M.D., F.R.C.S., for their essays on the aetiology, investigation, and treatment of renal calculus.

The Cartwright Prize for 1960 was awarded to Mr. G. L. Howe, F.D.S. R.C.S., M.R.C.S., L.R.C.P., and a certificate of Honourable Mention to Mr. H. P. Cook, F.D.S. R.C.S., for their essays on the role of surgical procedure in relation to dental prosthetic problems.

The election of Professor W. W. Mushin as Dean and the re-election of Dr. H. J. V. Morton as Vice-Dean of the Faculty of Anaesthetists for the ensuing year from June 28, 1961, was reported.

The election of Professor T. C. Gray, Dr. C. F. Scurr, and Dr. J. D. Robertson to the Board of the Faculty of Anaesthetists for the ensuing eight years was reported.

Dr. M. S. Israel was appointed Lecturer in Microbiology in the Department of Pathology.

The Evelyn Sprawson Prize was awarded to Mr. James Jepson Mather, of Guy's Hospital Dental School.

The following were elected Fellows of the College without examination as medical practitioners of twenty years' standing: Dr. R. A. S. Cory, Dr. E. Rohan Williams, Sir Eric Wilfred Fish, Professor R. A. Willis, Dr. L. Guttman, Group Captain A. L. Knipe.

The following were elected Fellows in the Faculty of Anaesthetists without examination: Professor M. S. el Hakeem, Dr. C. Stanley Jones, Dr. L. H. Lerman, Dr. O. I. E. Nicholson, Dr. V. Rajagopalan.

A Diploma of Fellowship was granted to J. W. Fisher.

A Diploma of Fellowship in the Faculty of Anaesthetists was granted to J. W. Lloyd.

Diplomas were granted, jointly with the Royal College of Physicians of London, as follows:

DIPLOMA IN OPHTHALMOLOGY.—Adeeb Saleeb, S. Anandarajan, J. R. S. Barton, J. Beaumont-Haynes, Shirley D. Campbell, A. Carroll, A. F. M. A. A. Chaudhury, Chin Mee Hong, I. A. Chisholm, A. M. Chowdhury, C. C. Constantinides, A. W. Craig, P. Dhir, W. H. G. Douglas, M. Erami, H. B. Fraser, R. E. R. Gillespie, C. P. Gupta, R. D. Hunter, G. J. Hussain, A. Islam, R. C. Jaiswal, O. A. H. Johnson, N. A. Khan, Ko Lay, U. Majzoub, Maung Myint Thein, M. A. Mirza, F. P. Morris, A. K. Mukherjee, C. J. Must, Mya Han, J. O. Odulate, D. Parker, N. A. Pathan, B. T. Pienaar, P. V. Pigott, R. M. Powrie, S. G. R. N. Rao, S. N. M. Rizk, Muriel E. Rolfe, D. Roychowdhury, D. W. Sabiston, J. P. Sarks, N. C. Singhal, D. M. Somerville, Kathleen M. Thomas, C. O. Thompson, Pamela M. Thorne, B. N. Tiwari, S. A. Wadud, P. H. Williams, S. M. Yahya, A. H. A. Yousif.

DIPLOMA IN MEDICAL RADIODIAGNOSIS.—D. H. Abbott, J. C. Anderson, L. E. Apiklan, O. P. Charlton, F. L. Cole, P. Dutton, R. H. Gibbon, J. N. Glanville, Z. Grahovac, D. C. Jackson, I. Kelsey Fry, R. T. McKay, J. Mitchell, N. L. Patel, S. H. Petros, J. M. Pinto, J. L. Price, M. D. Rawson, S. P. Smith, P. Sneider, I. D. Thompson, M. B. Warakaulle.

DIPLOMA IN MEDICAL RADIOTHERAPY.—C. D. Collins, G. J. A. Edelstyn, J. I. Gold, F. A. Ll. Kircher, Edna Matthews, E. R. Monypenny, E. A. Ramanayake, Priscilla A. Ridge, Margery Williams.

DIPLOMA IN CHILD HEALTH.—I. Ahmed, A.-R. A. Akta, A. J. R. Anderson, A. Animashaun, Judith M. Babb, D. B. Bannerjee, Winifred M. Bartindale, K. Bass, G. J. Biggam, J. A. Brown, Doreen R. G. Browne, M. P. Buckley, Hilda D. Bune, S. Bunni, A. K. Chacko, Kim Yong Chan, Brenda M. Chant, N. A. Coutts, A. S. Day, R. B. Deering, Ann C. Denchar, J. A. Dodge, Elizabeth Duane, Iris M. Duke, Angela K. Earls, A.-H. M. El-Shaboury, Beryl H. Evans, F. F. Fenech, M. T. Fernandes, R. M. A. Fernando, Jean M. Firth, C. E. Forbes, Anna L. Frenkiel, G. B. Gasson, G. S. Gilchrist, Gay J. Gillibrand, I. B. P. Glaun, C. B. T. Grant, R. C. Gupta, R. C. Gupta, S. P. Gupta, J. R. Harper, J. T. Harries, M. Z. Hasan, G. Hass, G. G. Hay, Jean Hellings, G. G. Hinton, Vijaya L. Hooja, T. W. Hoskins, J. M. Ibrahim, Sylvia R. Ingold, Tit Shing Ip, S. Jayaratne, Sumithra Jayaweera, G. Jeganathan, Rosemary A. Johnson, Jocelyne D. L. Kane-Berman, E. K. Karunakaran, Rena D. Katz, Kala M. Kewalramani, Hilary R. G. Lennox, Y. Lutwama, M. S. Madan, D. Mahafanabis, K. S.

Mankoo, J. Martin, Moira S. Meldrum, C. G. Miller, Agnes M. Mills, June Mills, A. R. L. Neil, Wing Hang Ng, O. C. Nwankwo, K. M. Parry, K. C. Patel, Wai-On Phoon, Lizette G. Potts, M. Q. Qureshi, Barbara J. Rashbass, Sylvia J. A. Raymond, E. O. R. Reynolds, Naomi S. Richman, Mary S. Rizk, E. U. Rosen, E. J. R. Rossiter, K. W. Rowden, Hermione B. Roxburgh, S. S. Sanders, Gloria H. Sands, I. B. Sardharwalla, R. S. C. Scoular, Khin-Khin Sein, C. A. Selway, W. G. Shakespeare, S. K. Shammaa, M. K. Sharif, S. H. Shirazee, Swadesh Sikka, W. S. A. Singh, Clare N. Smith, Jacqueline A. K. Smith, P. Sunakorn, G. B. Sutton, A. Swain, N. A. Syed, Reni W. Tents, K. Thirunavukkarasu, Ena E. Thomas, J. G. Thomas, N. E. Thomas, W. M. S. Thomson, Rita C. Travers, Yen-Chow Tsao, Jill P. Wayland, B. S. Wilson, Marie B. Wilson, Susan E. J. Young, H. A. Zarnegar.

DIPLOMA IN PHYSICAL MEDICINE.—H. D. Adler, Norma A. Beardwell, M. I. Bruk, E. N Glick, Ma Mya Sein.

DIPLOMA IN TROPICAL MEDICINE AND HYGIENE.—C. D. Addo, S. P. Ahuja, O. P. Arya, E. S. W. Bidwell, N. A. Boyd, R. S. Britton, Beatrice M. Brown, A. D. M. Bryceson, A. W. Burdon, M. A. Chishti, E. W. Dade, B. C. Das, I. A. A. De Coutere, C. De Silva, S. Dhamavaratha, H. Elamin, R. W. Emmons, Z. S. Farid, A. K. Foli, C. W. Free, C. J. Garrett, J. Gray, L. M. Hambraeus, S. Hannoudi, S. A. Janmohamed, M. L. Johnson, W. G. Johnston, J. B. Kelly, R. S. A. Khan, P. N. Kochhar, A. A. Khawaja, J. J. U. Laine, M. I. Lander, R. Marks, S. F. Meerza, R. J. Moylan-Jones, M. G. O. Parrish, N. A. Pathan, P. B. Pickles, C. R. M. Prentice, M. Raza, S. A. S. Rizvi, R. D. C. Southcott, J. H. Taylor, J. Li. E. W. Thomas, G. W. Thompson, A. D. Whanger.

DIPLOMA IN PSYCHOLOGICAL MEDICINE.—R. A. Flood.

After the meeting a Hunterian Lecture was delivered by Professor T. J. Butler on the effect of gastrectomy on pancreatic function in man.

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

The following candidates were successful at the recent examination for the Dublin Diploma in Obstetrics:

I. E. E. A. Aboul-Magd, E. J. T. Giblin, R. W. J. R. James, K. T. Maphathe, A. Meade H. B. Miller, R. Omar, S. Sulochana, A. A. Shaikh, J. P. Walsh.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

At a meeting of the Council of the College held on March 15, with the President, Mr. A. C. H. Bell, in the chair, the Rt. Hon. R. G. Menzies, P.C., C.H., Q.C., was admitted to the Honorary Fellowship of the College.

ROYAL AUSTRALASIAN COLLEGE OF SURGEONS

At the Primary examination for Fellowship of the College, held in Melbourne and Dunedin in March, the following candidates were approved:

G. S. Adams, W. A. J. Campbell, C. P. Clarke, Ll. S. Coats, B. G. D. Cohen, B. T. Collopy, Margaret M. Davis, D. J. Gillett, R. J. Hall, A. T. Hosking, J. F. Ledischke, H. J. Lorbeer, L. G. Lukin, Ruth V. Magnus, J. W. Mewett, P. J. Morris, P. G. Petty, P. J. Phillips, J. P. Royle, I. A. Shumack, D. H. Thomas.

At the Primary examination for Fellowship of the Faculty of Anaesthetists of the College, held in Melbourne and Dunedin in March, the following candidates were approved:

D. C. T. Bush, J. R. Hankey, Beryl E. Jack, D. J. Taylor.

Vital Statistics

Infectious Diseases

Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

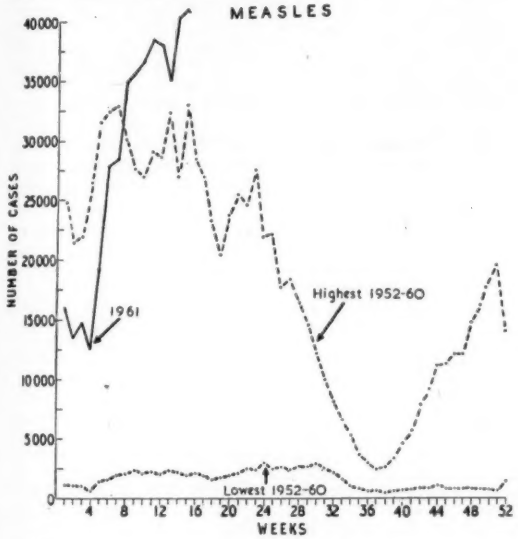
	Week Ending April 15	Week Ending April 22
Acute Poliomyelitis		
Suffolk	5	3
Ipswich C.B.	4	3
Staffordshire	0	4
West Bromwich C.B.	0	3
Warwickshire	1	3
Birmingham C.B.	1	3
Paratyphoid Fever		
Lancashire	0	14
Manchester C.B.	0	8
Stretford M.B.	0	4
Diphtheria		
London	3	4
Battersea	3	2
Warwickshire	1	5
Birmingham C.B.	1	5
Measles		
Devonshire	295	360
Plymouth C.B.	150	217
Durham	1,491	1,374
Gateshead C.B.	230	267
Essex	2,999	1,952
Southend-on-Sea C.B.	116	127
Thurrock U.D.	177	181
Hampshire	2,589	1,566
Southampton C.B.	260	331
Kent	1,708	1,336
Orpington U.D.	98	107
London	2,391	1,881
Islington	119	135
Lambeth	152	172
Middlesex	2,629	1,942
Sunbury on Thames U.D.	84	103
Nottinghamshire	474	500
Nottingham C.B.	177	273
Staffordshire	2,368	1,976
Walsall C.B.	257	273
Aldridge U.D.	87	146
Surrey	1,675	1,404
Guildford M.B.	89	124
Walton and Weybridge U.D.	73	102
Warwickshire	2,678	2,137
Rugby M.B.	123	128
Solihull M.B.	143	159
Worcestershire	557	457
Kidderminster M.B.	87	108
Yorkshire West Riding	2,830	2,147
Bradford C.B.	108	112
Huddersfield C.B.	250	253
Glamorganshire	900	824
Cardiff C.B.	391	472
Monmouthshire	143	343
Newport C.B.	143	154
Dysentery		
Devonshire	5	14
Exeter C.B.	5	13
Essex	33	22
Lancashire	88	69
Liverpool C.B.	3	19
Crosby M.B.	0	14
Leicestershire	6	13
Leicester C.B.	6	13
London	60	39
Norfolk	3	14
Blofield and Flegg R.D.	0	13
Suffolk	6	10
Ipswich C.B.	3	10
Yorkshire West Riding	88	79
Leeds C.B.	21	32
Glasgow	77	76
Edinburgh	26	22
Dundee	10	16

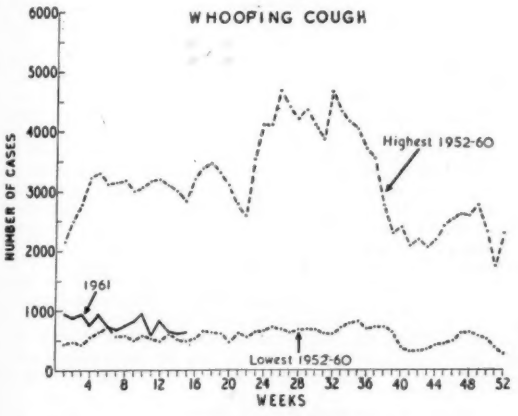
England and Wales in First Quarter

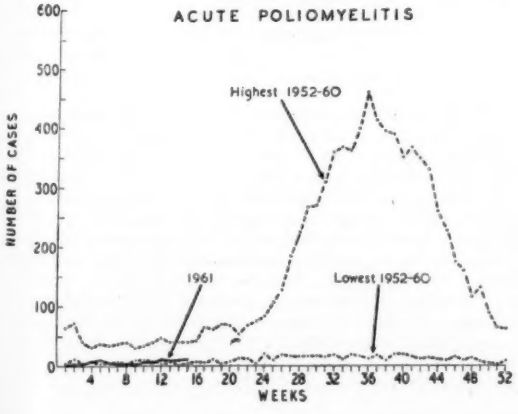
More births were registered in the first quarter of 1961 than in any first quarter since 1947. They numbered 203,976, giving a rate of 18.1 per thousand population. Deaths registered in the first quarter numbered 176,917, giving a rate of 15.7 per thousand population. The rates for the first quarters of 1960 and 1959 were 13.1 and 15.8. The infant mortality rate was 22.9 per thousand live births; this compares with a rate of 23.2 for the first quarter of 1960. The stillbirth rate was 18.9 per thousand live and stillbirths; in the corresponding quarters of 1960 and 1959 the rates were 19.7 and 21.6.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1952–60 are shown thus ------, the figures for 1961 thus ———. Except for the curves showing notifications in 1961, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **April 15** (No. 15) and corresponding week 1960.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	7	3	1	0		3	1	0	0	
Dysentery ..	486	60	147	21		1,745	222	180	21	3
Encephalitis, acute	1	0		0		2	0	1	0	
Enteric fever:										
Typhoid ..	1	0	0	0		1	0	0	0	
Paratyphoid ..	5	0	6 (B)	2		0	0	0	0	
Food-poisoning ..	123	20	3	1		131	11	10	0	
Infective enteritis or diarrhoea under 2 years				10					2	18
Measles*	41,003	2391	397	571		2,121	81	35	1	53
Meningococcal infection	23	1	7	1		12	1	3	1	
Ophthalmia neonatorum	19	1	2	0		22	2	3	0	
Pneumonia† ..	275	21	195	11		297	10	147	0	2
Poliomyelitis, acute:										
Paralytic ..	8	0	} 0	0		{ 2	1	0	} 0	2
Non-paralytic ..	1	0				2	0	0		
Puerperal fever§ ..	172	29	7	0		159	21	6	1	
Scarlet fever ..	397	29	23	21		794	36	34	20	10
Tuberculosis:										
Respiratory ..	429	46	112	14		375	47	52	24	
Non-respiratory	75	8	16	4		50	3	9	4	
Whooping-cough	635	23	33	5		691	59	167	6	27

DEATHS	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	1	0	0	0	0	0
Dysentery ..	0	0		0		0	0		0	
Encephalitis, acute		0			0		1			0
Enteric fever ..	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	4	0	0	0	0		0	0	1	0
Influenza	23	0	1	0	2	29	1	1	0	2
Measles		1	2	0	3	0	0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia ..	600	52	21	19	7	626	47	25	13	11
Poliomyelitis, acute	1	0		0	0	1	0		0	0
Scarlet fever ..		0	0	0	0	0	0	0	0	0
Tuberculosis:										
Respiratory ..	} 73	{ 8	} 4	{ 0	3	} 63	{ 4	5	2	0
Non-respiratory		0		1	1		1	2	0	0
Whooping-cough	1	0	0	0	0	3	0	1	0	0
Deaths 0–1 year ..	355	35	30	12	11	300	29	29	4	8
Deaths (excluding stillbirths) ÷ ..	10,399	786	649	150	177	9,804	736	574	116	106
LIVE BIRTHS ..	16,420	141	1020	292	537	11,944	1032	785	264	293
STILLBIRTHS ..	335	28	22			296	28	29		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia

Medical News

Prime Minister of Sierra Leone

[Central Press Photos, Ltd.

Sir MILTON MARGAI, the Prime Minister and Minister for Internal Affairs and Development of Sierra Leone, which has recently celebrated its independence, was educated at Albert Academy and Fourah Bay College, Freetown, and graduated in medicine at the University of Durham in 1926. He spent a year in private practice before becoming Government Medical Officer in his own country in 1928, a post which he held until 1950. He founded and led the People's Party, the first party to form a Government under the then new constitution. From 1953 to 1954 he held the post of Minister of Health, Agriculture, and Forestry before becoming Premier. Sir Milton, who is 65, was knighted in 1959.

Rockefeller Foundation Grants

During the first four months of this year Rockefeller Foundation grants totalled $3,593,995, of which $1,015,951 went to the medical and natural sciences. The London School of Hygiene and Tropical Medicine receives a grant of £50,000 up to June, 1966, for an intensified research programme on bilharziasis in co-operation with Makerere College, Kampala, Uganda, which will serve as a base for the clinical work, and the East African Medical Research Council, which will provide the core of the field staff. Dr. J. W. S. HARRIS, lecturer in anatomy, London Hospital Medical College, receives a Fellowship for study in the United States. A five-year grant of £10,000 will assist a faculty exchange programme between University College, Ibadan, Nigeria, and the medical schools at Dakar, Senegal; Leopoldville, Congo; Khartum, Sudan; and Kampala, Uganda. Research on uterine physiology is being supported in Uruguay; on Kumlinge disease virus in Finland; and on cell physiology in Bogotá, Colombia. Help is being given for expanding teaching and research programmes in the Faculty of Medicine, University of Rio Grande do Sul, Brazil, and in the Faculty of Medicine, University of San Marcos, Lima, Peru.

Regional Hospital Board Appointments

The following are among those appointed or reappointed as members of the 15 regional hospital boards in England and Wales:

Newcastle: Mr. D. C. DICKSON, *Leeds:* Colonel G. ARMITAGE.* *Sheffield:* Professor J. G. MCCRIE, Dr. G. C. WELLS-COLE. *East Anglia:* Dr. A. J. R. F. JOHNSON, Dr. J. V. MORRIS. *North-west Metropolitan:* Dr. ANNIS GILLIE, Dr. H. JOULES, Dr. J. S. B. LEWIS, Professor R. E. O. WILLIAMS.* *North-east Metropolitan:* Dr. C. ALLAN BIRCH. *South-east Metropolitan:* Mr. J. C. F. LLOYD WILLIAMSON.* *South-west Metropolitan:* Dr. G. W. GARLAND, Dr. T. P. REES. *Oxford:* Mr. G. T. WILLOUGHBY CASHELL, Dr. A. W. HENDERSON, Dr. R. G. MCINNES.* *South-western:* Dr. H. L. SHEPHERD, Dr. G. STEWART-SMITH, Dr. S. NOY SCOTT.* *Welsh:* Mr. IVOR LEWIS, Dr. D. E. PARRY-PRITCHARD, Professor W. W. MUSHIN.* *Birmingham:* Dr. J. C. HEATHER, Professor T. MCKEOWN, Dr. J. J. O'REILLY, Dr. S. R. F. WHITTAKER. *Manchester:* Mr. T. S. HESLOP, Professor W. I. C. MORRIS. *Liverpool:* Dr. D. BROWN, Dr. C. H. WALSH.* *Wessex:* Dr. A. J. GALBRAITH, Dr. I. A. MACDOUGALL. (*New member.)

Provincial Teaching Hospital Appointments

The following are among those appointed or reappointed as members of the boards of governors of the 10 provincial teaching hospitals in England and Wales:

United Newcastle Hospitals: Professor A. G. R. LOWDON, Professor S. D. M. COURT,* Dr. A. G. OGILVIE.* *United Leeds Hospitals:* Professor R. E. TUNBRIDGE, Dr. S. T. ANNING,* Professor S. J. HARTFALL,* Mr. A. B. PAIN.* *United Sheffield Hospitals:* Professor J. G. MCCRIE, Professor G. L. ROBERTS, Mr. W. HYNES,* Professor G. M. WILSON.* *United Cambridge Hospitals:* Dr. L. B. COLE, Dr. R. I. N. GREAVES, Professor J. S. MITCHELL, Dr. E. BERESFORD DAVIES.* *United Oxford Hospitals:* Mr. P. R. ALLISON, Mr. E. W. PEET,* Dr. A. W. WILLIAMS.* *United Bristol Hospitals:* Dr. R. H. BUTCHER, Professor C. B. PERRY, Dr. J. H. MIDDLEMISS,* Dr. J. E. G. PEARSON.* *United Cardiff Hospitals:* Dr. A. TREVOR JONES, Mr. R. G. MALIPHANT, Professor A. G. WATKINS.* *United Birmingham Hospitals:* Professor A. L. D'ABREU, Dr. A. BEAUCHAMP, Dr. J. C. HEATHER, Professor T. MCKEOWN, Dr. A. B. TAYLOR, Professor Sir ARTHUR THOMSON. *United Manchester Hospitals:* Dr. W. CHADWICK, Dr. R. W. LUXTON, Professor Sir ROBERT PLATT, Professor W. SCHLAPP, Dr. E. A. GERRARD,* Mr. W. F. NICHOLSON.* *United Liverpool Hospitals:* Mr. J. M. LEGGATE, Mr. R. SELBY, Dr. R. W. BROOKFIELD,* Dr. A. THELWALL JONES.* (*New member.)

London Teaching Hospital Appointments

The following are among those appointed or reappointed members of the boards of governors of the 26 London teaching hospitals:

St. Bartholomew's Hospital: Mr. F. C. W. CAPPS, Dr. F. GRAY,* Mr. C. NAUNTON MORGAN.* *London Hospital:* Dr. H. BLIGHT MAY, Mr. D. G. RITCHIE, Dr. J. STANLEY THOMAS, Dr. W. W. BRIGDEN,* Professor V. W. DIX.* *Royal Free Hospital:* Dr. R. D. DEWAR, Dr. G. C. STEEL, Professor KENNETH R. HILL.* *University College Hospital:* Mr. J. D. S. FLEW, Mr. M. L. FORMBY, Dr. E. A. BLAKE PRITCHARD.* *Middlesex Hospital:* Dr. H. M. C. MACAULAY, Mr. P. HARKER NEWMAN.* *Charing Cross Hospital:* Dr. A. DOYNE BELL, Dr. E. C. WARNER.* *St. George's Hospital:* Dr. M. I. A. HUNTER, Dr. D. STARK MURRAY, Dr. K. ROBSON. *Westminster Hospital:* Dr. F. DUDLEY HART, Mr. F. A. D'ABREU.* *St. Mary's Hospital:* Dr. J. GREEN, Mr. R. MCIVER PATON, Dr. THOMAS A. KEMP.* *Guy's Hospital:* Dr. E. R. BOLAND, Mr. GRANT MASSIE, Dr. A. TALBOT ROGERS, Mr. E. G. SLESINGER, Dr. W. N. MANN.* *King's College Hospital:* Dr. F. S. COOKSEY, Dr. V. F. HALL, Dr. A. FISHER MCMILLAN, Sir JOHN H. PEEL. *St. Thomas's Hospital:* Mr. G. H. BATEMAN, Mr. R. W. NEVIN, Dr. J. FOREST SMITH, Mr. T. W. MIMPRISS.* *Hammersmith, West London, and St. Mark's Hospitals:* Professor J. MCMICHAEL, Dr. C. E. NEWMAN. *Hospital for Sick Children:* Mr. J. CROOKS, Professor A. MONCRIEFF, Dr. A. P. NORMAN. *National Hospitals for Nervous Diseases:* Professor A. KEKWICK, Dr. E. A. BLAKE PRITCHARD. *Royal National Throat, Nose, and Ear Hospital:* Mr. C. GILL-CAREY. *Moorfields Eye Hospital:* Sir STEWART DUKE-ELDER, Mr. T. KEITH LYLE, Mr. S. J. H. MILLER.* *Bethlem Royal and Maudsley Hospitals:* Sir W. ALLEN DALEY, Dr. D. L. DAVIES, Dr. W. LINFORD REES. *St. John's Hospital for Diseases of the Skin:* Dr. H. J. WALLACE. *Hospitals for Diseases of the Chest:* Dr. W. E. LLOYD, Dr. JOSEPH SMART, Sir GEOFFREY TODD, Dr. J. R. BIGNALL.* *Royal National Orthopaedic Hospital:* Mr. H. J. BURROWS, Mr. DAVID TREVOR.* *National Heart Hospital:* Dr. G. W. HAYWARD, Dr. G. H. JENNINGS, Dr. P. H. WOOD. *St. Peter's, St. Paul's, and St. Philip's Hospitals:* Mr. J. G. SANDREY. *Royal Marsden Hospital:* Mr. R. W. RAVEN, Professor D. W. SMITHERS, Dr. A. M. CHESTER.* *Queen Charlotte's and Chelsea Hospitals:* Mr. A. C. BELL, Mr. S. G. CLAYTON.* *Eastman Dental Hospital:* Miss K. G. LLOYD-WILLIAMS, Professor HOMER C. KILLEY.* (*New member.)

Poliomyelitis Vaccination Fourth Doses

The Minister of Health has asked local health authorities to extend their arrangements for vaccination against poliomyelitis to provide a fourth injection of inactivated poliovirus vaccine for certain younger children.

"Abstracts of Efficiency Studies in the Hospital Service"

The Ministry of Health has prepared a series of pamphlets dealing with money-saving ideas which are the fruits of work done by organization and method and work study officers in the hospital service. The pamphlets will appear in sets at intervals throughout the year and will cost 12s. 6d. a year from H.M.S.O. The present set covers "Dental Work" (1); "Linen Services (Planning an Area Laundry)" (2); "Linen Services (Sewing Room Work)" (3); "Pathology Department (Delivery of Specimens to Laboratory)" (4); "Pathology Department (Photographic Reproduction of Reports)" (5); "Pharmacy Department (Layout of a Dispensary)" (6); "Transport (Group Transport System)" (7).

Royal College of Physicians' Rheumatism Report

The Royal College of Physicians' reconstituted Committee on Chronic Rheumatic Diseases has been considering in the light of developments in the last decade the further implications of a report issued by a similar committee in 1951. The 1961 report says that there is increasing evidence of the part played by the rheumatic diseases in causing disability and incapacity for work, and believes that there are not enough medical consultants with the appropriate experience, and that beds and adequate out-patient facilities for the more serious and difficult cases are not always available. The previous report recommended the establishment of special centres, but only two, Sheffield and Stoke Mandeville, have been founded since 1950, and the position and future of those working there were not made sufficiently clear in the 1951 report. Few consultant posts in rheumatology have been established in the National Health Service, and more than half of those trained in the United Kingdom have gone overseas, where senior posts in the specialty are available. The committee's main recommendations are that every Hospital Region should have a special rheumatic centre under a consultant in rheumatology, which in addition to treatment would undertake clinical research and lecturing; that a number of consultant clinical appointments in rheumatology should be made within the N.H.S., those appointed having usually completed eight years of postgraduate work including several years devoted to rheumatology; that in every main hospital group an appropriately trained general physician should devote himself in part to rheumatic diseases; and that every effort should be made to encourage and support the home care of patients by the general practitioner. The chairman of the reconstituted committee was Dr. W. S. C. COPEMAN, and the honorary secretary Dr. G. D. KERSLEY.

Prescribed Industrial Diseases

The list of prescribed industrial diseases has been extended to include ocular ochronosis due to exposure to quinone or hydroquinone. A person contracting the disease at work will be covered for the benefits of the Industrial Injuries Scheme from April 28. (The National Insurance (Industrial Injuries) Prescribed Diseases) Amendment Regulations, 1961, S.I., 1961, No. 691, H.M.S.O. or booksellers, price 3d.)

Chelsea Clinical Society

The annual dinner of the Chelsea Clinical Society was held on April 25 at the Hall of the Society of Apothecaries, with Sir JOHN PEEL, the president, in the chair. The toast to the Society was proposed by Lord EVERSHED, Master of the Rolls, who mentioned that among his eminent predecessors was a surgeon, Mr. Henry Bickersteth, later Lord Langdale, who took up law, became Master of the Rolls in the nineteenth century, and successfully persuaded the Government to provide an adequate repository for the national records. Sir JOHN PEEL, in reply, described the activities of the Society during the past year and welcomed the guests. The evening ended with the inauguration of the president for the new session, Mr. WARREN HARVEY.

Association of British Pharmaceutical Industry

Speaking at the annual dinner of the Association of the British Pharmaceutical Industry, the Minister of Health, Mr. J. ENOCH POWELL, said that the policy he was pursuing was one neither subservient nor inimical to the industry. On behalf of the National Health Service he was the industry's customer for about one-third of its production. But he was no ordinary customer, for though he paid the bill he neither ordered nor consumed the goods; they were ordered by doctors and consumed by patients. There were broadly two lines of policy open to the Minister. One was for him as customer to try to manage the supplier, or even to make a take-over bid for him. This was a policy Mr. Powell repudiated equally on practical and political grounds. The alternative was to do all they could to reproduce the conditions of a normal supplier–customer relationship in the circumstances created by the N.H.S. The medical profession was being helped by a group of measures to prescribe "in a manner which combines the highest interest of the patient with regard to the fact that articles have a cost and a varying cost." In reply to the Minister, Mr. H. W. PALMER, president of the A.B.P.I., said that it was impossible for the industry to rest happy with a situation in which on many occasions the industry had been charged with responsibility for a state of affairs where control lay in the fields of social policy and political science and hardly at all in those of research policy and pharmaceutical enterprise.

People in the News

Mr. ARNOLD WALKER has been re-elected as chairman and Professor A. A. MONCRIEFF as deputy chairman of the Central Midwives Board for the ensuing year.

Mr. W. DEMPSTER, of the department of experimental surgery at the Postgraduate Medical School of London University, is making a British Council working visit to Hungary at the invitation of the Hungarian Academy of Sciences.

COMING EVENTS

B.B.C. Sound.—"To Speculate Shrewdly," May 7, 9.30 p.m. (Home). Round-table discussion between Sir MACFARLANE BURNET, Professor P. B. MEDAWAR, Professor W. F. LIBBY, and Professor D. A. GLASER, recorded in Sweden at the recent Nobel prize-giving.

Hospitals' Symphony Orchestra.—Concert, May 13, Dukes Hall, Royal Academy of Music, Marylebone Road, London. Admission by programme obtainable from ROBERT TATE, Guy's Hospital Medical School, London S.E.1.

London Amateur Boxing Association.—Meeting of London A.B.A. Medical Advisory Panel, May 17, 8 p.m., British Railways Film Unit, Savile Row, London W.1, films, discussion, and refreshments.

Harveian Society of London: Buckston Browne/Gray Hill Memorial Dinner.—May 24, Members' Dining Room, House of Commons. Guided tours, 6.30 p.m.; sherry, 7.15 p.m.; dinner, 7.45 p.m. Tickets (members 1 guinea, guests 2 guineas) from Honorary Secretaries, 11 Chandos Street, London W.1, by May 12.

Moynihan Lecture.—Sir HARRY PLATT, "Moynihan, the Education and Training of the Surgeon," May 25, 3 p.m., Riley Smith Hall of Leeds University Union.

Biochemical Society.—406th meeting, May 25, 26, Dublin. Original communications: at University College, May 25, 10 a.m.–12.45 p.m., and May 26, 2–4.30 p.m.; at Trinity College, May 26, 10.30 a.m.–12.30 p.m. Followed on May 27, 10 a.m., by meeting of Association of Clinical Biochemists at University College, and symposium on "Acid-base Balance"; 2.15 p.m., original communications.

British Society for Immunology. — Symposium, "Immunity to Protozoa," June 1, 2, Edward Lewis Theatre, Middlesex Hospital Medical School, Cleveland Street, London W.1.

Chest and Heart Association.—Conference, "Stroke Rehabilitation," June 22, 10 a.m.–5 p.m., Livery Hall, Guildhall, London E.C.2. Chairman, Professor C. BRUCE PERRY. Fee (including buffet lunch) 2 guineas. Details from Chest and Heart Association, Tavistock House North, Tavistock Square, London W.C.1.

Association of Industrial Medical Officers.—Annual provincial meeting, Belfast, June 26–June 30. Medical symposia: "Electronics," "The Effects of High Unemployment Rates," and "The Linen Industry," Queen's University of Belfast. Details from Association of Industrial Medical Officers, 47 Lincoln's Inn Fields, London W.C.2.

Imperial College of Science and Technology and London School of Hygiene and Tropical Medicine.—One-year full-time postgraduate courses in public health engineering for students with degree in civil engineering or equivalent. Details from the Registrar, Imperial College of Science and Technology, London S.W.7.

3rd International Congress of Dietetics.—"Tradition, Science, and Practice in Dietetics," July 10–14, Church House, Westminster, London S.W.1. Details from Congress Secretariat, 251 Brompton Road, London S.W.3.

International Symposium on Audiosurgery.—Madrid, August 2–4. Organized by National School of Medicine, National Institute of Medicine, and Centre of Surgical Specialities. Subjects: "Audiosurgery of Congenital Defects of the Ear," "Chronic Suppurative Processes of the Ear and Their Sequelae," "Otosclerosis," and "Surgery of the Facial Nerve." Details from Dr. A. JUDERIAS, Centro Nacional de Espedialidades Quirurgicas, Ciudad Universitaria, Madrid, Spain.

2nd International Congress on Mental Retardation.—Vienna, August 14–19. Details from Congress Secretariat at University Children's Clinic, 14 Lazarettgasse, Vienna 9, Austria.

5th World Assembly of Israel Medical Association.—Jerusalem, Haifa, and Tel Aviv, August 14–25. Details from General Secretary of Assembly, P.O. Box 1342, Jerusalem, Israel.

1st International Pharmacological Meeting.—Stockholm, August 22–25. General theme: "Mode of Action of Drugs." Details from meeting's secretariat at Karolinska Institut, Stockholm 60, Sweden.

NEW ISSUES OF SPECIALIST JOURNALS

*The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.*1.

BRITISH JOURNAL OF PREVENTIVE AND SOCIAL MEDICINE

Pulmonary Ventilatory Functions of Coalminers in Various Areas in Relation to the X-ray Category of Pneumoconiosis. A. L. Cochrane and I. T. T. Higgins, with the assistance of Jacob Thomas.
Theory and Observation in Family Epidemics of the Common Cold. M. A. Heasman and D. D. Reid.
Social Class and Prognosis in Schizophrenia. Part I. B. Cooper.
Social Class and Prognosis in Schizophrenia. Part II. B. Cooper.
Prostitution and Venereal Disease. Social Considerations of Prostitution. R. R. Willcox.

Volume 15, No. 1. (Quarterly; £3 annually.)

BRITISH JOURNAL OF INDUSTRIAL MEDICINE

"Sooty Manchester" and the Social-Reform Novel 1845-1855. Arthur Pollard.
Chronic Respiratory Disease in a Random Sample of Men and Women in the Rhondda Fach in 1958. I. T. T. Higgins and A. L. Cochrane.
Carbon Pneumoconiosis. A. A. Miller and F. Ramsden.
Carbon Pneumoconiosis in a Synthetic Graphite Worker. W. B. Lister.
Byssinosis Among Cotton Workers in Belgium. E. Tuypens.
The Role of Bacterial Endotoxins in Occupational Diseases Caused by Inhaling Vegetable Dusts. B. Pernis, E. C. Vigliani, C. Cavagna, and M. Finulli.
Histamine Liberation by Cotton Dust Extracts: Evidence Against its Causation by Bacterial Endotoxins. H. Antweiler.
Chronic Pulmonary Berylliosis in a Female Chemist. R. I. McCallum, I. Rannie, and C. Verity.
Observations on the Pathogenesis of Silicosis by Means of the Diffusion Chamber Technique. A. G. Heppleston, K. A. Ahlquist, and D. Williams.
The Effects of Vole Bacillus Vaccination of African Mine Workers in the Northern Rhodesian Copper Mines. R. Paul.
Cerebral Tumour in a Lead Worker. R. W. Portal.
Miscellanea:
Preliminary Communication: A Physiological Study of the Effects of Vibration on the Fingers. Ladislaus Magos.
Expired Air Resuscitation in a Contaminated Atmosphere. W. M. Dixon, A. Ward Gardner, and B. G. B. Lucas.
Book Reviews.

Volume 18, No. 2. (Quarterly; £3 annually.)

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, May 8

INSTITUTE OF DERMATOLOGY.—At British Institute of Radiology, 5 p.m., Dr. L. Szur: Radiotherapy of Benign Skin Conditions.
INSTITUTE OF NEUROLOGY.—5.30 p.m., Dr. E. J. Moran Campbell: Neurology of Respiration.
PLYMOUTH MEDICAL SOCIETY.—At North Friary House, 8.30 p.m., annual general meeting.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Professor J. R. Squire: Hypogammaglobulinaemia in Great Britain.
ST. MARY'S HOSPITAL MEDICAL SCHOOL: WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY.—5 p.m., Second Almroth Wright Lecture by Dr. S. Brenner: Bacteriophage Growth.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, Gower Street, W.C., 5 p.m., public lecture by Professor A. Neuberger, F.R.S.: Biosynthesis of Porphyrins and Chlorophylls—(1) Early Stages of the Biosynthesis.

Tuesday, May 9

BIRMINGHAM MEDICAL INSTITUTE: SECTION OF PSYCHIATRY.—8 p.m., Dr. Maurice Partridge: Mistakes and Mishaps.
ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Croonian Lecture by Professor John McMichael, F.R.S.: Reorientation in Hypertensive Vascular Disorders.
ROYAL COLLEGE OF SURGEONS OF EDINBURGH.—5 p.m., Professor D. C. Sabiston (Baltimore): Studies on Basic Principles in Vascular Surgery.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute, 5 p.m., Dr. C. M. Flood: To Book or Not to Book Home or Hospital Confinements.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. E. H. Larkin: Drug Treatment in Psychiatry.

Wednesday, May 10

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. K. V. Sanderson: Experimental Carcinogenesis and Clinical Cancer of the Skin.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. L. Livingstone: Idiopathic Interstitial Pulmonary Fibrosis.
LEWISHAM GENERAL HOSPITAL.—5.45 p.m., Dr. J. S. Staffurth: Physiological Basis of Radioiodine Investigations.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. W. H. McMenemey: Pathology of Encephalitis.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF PHARMACOLOGY.—At Physiology Theatre, Gower Street, W.C., 5.30 p.m., public lecture by Professor P. Bálint (Budapest): Reliability of Clearance Tests in the Evaluation of Renal Blood Flow.

Thursday, May 11

ALFRED ADLER MEDICAL SOCIETY.—At Medical Society of London, 8 p.m., Dr. A. K. Graf: Helping the Delinquent Child. A discussion will follow.
BRITISH INSTITUTE OF RADIOLOGY.—7.30 p.m., annual general meeting; 8 p.m., Mackenzie Davidson Memorial Lecture by Dr. F. Campbell Golding: The Forgotten Joint—the Shoulder.
HONYMAN GILLESPIE LECTURES.—At Anatomy Theatre, University New Buildings, Teviot Place, Edinburgh, 5 p.m., Mr. D. C. Sabiston, jun.: Surgery of the Coronary Circulation.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. R. M. Harman: Anatomy of the Skin and Benign Skin Conditions Treated by Radiation.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. A. Hollman: Diagnostic Methods in Heart Disease.
ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Croonian Lecture by Professor John McMichael, F.R.S.: Reorientation in Hypertensive Vascular Disorders.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Bland-Sutton Lecture by Dr. Frank Stansfield: Sir John Bland-Sutton, 1855-1936. His Life, Habits, and Friends.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. Desmond Curran: Postgraduate Demonstration in Psychiatry.
SOCIETY OF MEDICAL OFFICERS OF HEALTH: WELSH BRANCH.—At B.M.A. House, 195 Newport Road, Cardiff, 7.45 p.m., joint meeting with B.D.A. Professor A. G. Watkins: Some Dental Problems in Paediatrics.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, Gower Street, W.C., 5 p.m., public lecture by Professor A. Neuberger, F.R.S.: Biosynthesis of Porphyrins and Chlorophylls—(2) Formation of the Macrocyclic Rings.

Friday, May 12

FACULTY OF RADIOLOGISTS.—At Royal College of Surgeons of England, 4.30 p.m., 6th Crookshank Lecture by Sir Lawrence Bragg, F.R.S.: Atomic Architecture of Protein Molecules.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. N. C. Oswald and Mr. O. S. Tubbs: clinical demonstration.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., open lecture and demonstration for trainees in the specialty. Mr. G. H. Howells: Significance of Orbital Swellings in Nasal Accessory Sinus Disease.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., Mr. L. T. Cotton: Aetiology and Pathology of Varicose Veins.

Saturday, May 13

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—At Lecture Room B, Addenbrooke's Hospital, symposium on Paediatrics: The "Allergic" Diseases in Childhood. *Morning*, 10.30 a.m., Dr. R. R. A. Coombs, Ph.D.: Simple Classification of Allergic Phenomena; 11.30 a.m., Dr. A. J. Rook: Eczema in Infants and Children; 12.15 p.m., Dr. Douglas Gairdner: Asthma in Childhood. *Afternoon*, 2.15 p.m., Dr. Janet Roscoe and other members of the Paediatric Staff will demonstrate clinical cases; 3.45 p.m., Dr. R. C. Roxburgh: Infant That Fails to Thrive.
YORKSHIRE SOCIETY OF ANAESTHETISTS.—At Pinderfields General Hospital, Wakefield, 10.30 a.m., Dr. John Colson: Basic Physical Techniques Used in the Prevention of Pulmonary Complications; 2 p.m., Dr. R. Bryce-Smith: Air in Anaesthesia.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Blench.—On April 17, 1961, to Drs. Athelstan and Pearl Blench, a son—David Athelstan.

DEATHS

Dodds.—On April 9, 1961, James Allan Dodds, L.D.S. R.C.S., L.M.S.S.A., of 28 Victoria Avenue, Didsbury, Manchester.
Finney.—On April 11, 1961, at his home, Barwood, Alderley Road, Wilmslow, Cheshire, Albert Ernest Finney, M.D., aged 85.
Hine.—On April 6, 1961, Francis Jopson Hine, M.R.C.S., L.R.C.P., formerly of Rochdale, Lancs, aged 39.
Kennard.—On April 11, 1961, at her home, 7 Pilgrims Lane, Hampstead, London N.W., Mary Lena Roach Kennard, M.R.C.S., L.R.C.P.
McFarlane.—On April 7, 1961, at Bournemouth, Hants, Wilfrid McFarlane, *M.C.* (and Bar), M.D., aged 84.
Scott.—On March 6, 1961, John Andrew Adamson Prinski Scott, M.R.C.S., L.R.C.P., of 41 The Causeway, Potters Bar, Middx, late of Fletcher House, 774 High Road, Tottenham, London N.
Thompson.—On April 12, 1961, at 84 Moorside North, Newcastle upon Tyne 4, Margaret Thompson, M.B., B.S. (formerly Swinburne).
Worthington.—On April 8, 1961, at Blandford, Dorset, Frank Worthington, D.S.O., O.B.E., M.B., B.Ch., Lieutenant-Colonel, R.A.M.C., retired, aged 80.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Luminous Eyes in Toy Animals

Q.—*A child aged 5 has a soft toy with luminous eyes. Is there any danger of radiation? This toy is slept with, and cuddled at all times.*

A.—The presence of a substance emitting penetrating radiation is not essential for making the eyes of toy animals shine in the dark. Indeed, it would be reprehensible for such material to be incorporated in playthings liable to be broken, dismembered, or even swallowed. While the existence of a hazard is, unfortunately, no guarantee that undesirable elements will never be used in toy-making, it is reassuring to be able to report that the luminous eyes of a woolly owl, recently acquired from abroad, gave no evidence of containing any radioactive material and that no penetrating radiation from them could be detected. The simplest test for a layman to make is to keep the toy in complete darkness for 5–6 hours and then examine it, still in the dark. If luminosity has persisted it would indicate that the source of activation was radioactive material; if the eyes no longer shine, no penetrating radiation is present.

Children Witnessing Indecent Exposure

Q.—*What attitude should a parent or a doctor adopt in dealing with a child who has been upset by witnessing indecent exposure by a strange man?*

A.—This is by no means an infrequent experience, and many children appear to suffer no ill effects. At all ages it should be dealt with by matter-of-fact sympathy for an unpleasant occurrence, neither making an issue or a secret of it. The rarity of men or boys who do this sort of thing should be emphasized. With older children this differentiation should be maintained, pointing out that it is the action of a weak or inadequate boy or man.

Such incidents are probably less disturbing in a child already wholesomely oriented towards sexual information. While this should not form the text for enlightenment of the uninformed, an opportunity should be taken fairly quickly to give the child appropriate information on these matters in a better context.

Aetiology of Mongolism

Q.—*The incidence of mongols among live births is varyingly estimated as between 1 in 500 and 1 in 700, although it is said to be much higher in older women. (1) Can this be interpreted that all, or most, women produce a small proportion of ova with chromosome abnormality, and that it is just a chance that the abnormal ovum becomes fertilized? (2) Is the abnormality related to women only or men as well?*

A.—(1) Probably most women, if not all, produce a proportion of ova with some kind of chromosome abnormality, and it is just chance whether these ova become fertilized.

(2) Chromosome abnormalities can probably occur in both sperms and ova. However, non-disjunction of chromosome 21, the most common cause of mongolism, is related to the mother's age rather than to the father's. There is no association of mongolism with the father's age if the mother's age is held constant. It may well be, however, in some cases, particularly when the mother is young, that the chromosome abnormality responsible for mongolism, whether non-disjunction or translocation, was present in the sperm rather than the ovum.

Mirror Writing

Q.—*A boy aged 7 has developed severe reading difficulties and mirror writing since starting school. Previously a confident, happy child, his trouble also manifests itself in fear of school, disobedience, and emotional upsets. What is the prognosis and treatment?*

A.—Mirror writing and reading difficulty at this age may represent a degree of immaturity that should improve with time. Mixed laterality may be associated. Competent psychological investigation is required, and special teaching techniques may be indicated. The degree of anxiety in relation to going to school suggests that other factors play a part. All aspects can be explored and dealt with at a child (guidance) psychiatric clinic. Alternatively the reading disability could be assessed and dealt with by an educational psychologist attached to the local education authority. On the basis of the available information the matter should be remediable.

Tranquillizers and the Foetus

Q.—*Is there any danger to the foetus or unborn child from the prolonged use of tranquillizers and anti-depressant drugs such as chlorpromazine, perphenazine, trifluoperazine, and similar preparations? I am not referring to the use of these drugs as anti-emetics in hyperemesis, but to their use in heavier dosage in psychotic cases.*

A.—Chlorpromazine and other similar tranquillizing drugs have been recommended for the treatment of the emotional disturbances of pregnancy, and it has also been suggested that they should be given prophylactically during pregnancy to schizophrenics who are in remission.[1] There is little doubt that these substances will cross the placental barrier, and that they may affect the foetus or unborn child. There is evidence that chlorpromazine affects the course of pregnancy in animals. Chambon[2] found that in rats it influenced the length of gestation and might cause abortion. Many of the offspring which survived were underdeveloped. These results suggest that the drugs should be used cautiously in pregnant women. Sobel,[3] however, who studied fifty-two women who had received chlorpromazine during pregnancy, found that there was not a higher incidence of foetal mortality or morbidity in these pregnancies compared with a control group. He did, however, find evidence which suggested that the administration of chlorpromazine in a daily dose of 500 mg. or more to women in the latter part of pregnancy was apt to cause respiratory distress in the newborn. This view is supported by Hodges and Bennett,[4] who advise against the use of chlorpromazine near term because of the unpredictable nature of the potentiation of other analgesics and anaesthetics which may be administered during labour. Sobel[3] also found that there was a slightly higher incidence of antepartum bleeding and premature births in his group of patients who had been treated with chlorpromazine.

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3 Sobel, D. E., *Arch. gen. Psychiat. (Chicago)*, 1960, **2**, 606.
4 Hodges, R. J. H., and Bennett, J. R., *J. Obstet. Gynaec. Brit. Emp.*, 1959, **66**, 91.

Long-term Oestrogens

Q.—*A young woman aged 29 has had a sub-total hysterectomy and bilateral oophorectomy for bilateral pseudomucinous cystadenomata. She is now having ethinyloestradiol 0.01 mg. by injection daily. Is this safe as a long-term replacement therapy?*

A.—In a case of this kind the aim should be to limit the period of oestrogen therapy to a few months, and not to continue it indefinitely. During this time the patient should be gradually weaned from oestrogens. When the oestrogen chosen is ethinyloestradiol it is pointless to give it parenterally. The need to have frequent injections may have an adverse psychological effect, and this preparation is equally active by mouth. In fact, the dose described is so small that the patient could probably manage well without

it. It is therefore suggested that treatment in this case be discontinued to see the effect. If true menopausal symptoms then develop, and if they are intolerable, but not otherwise, oestrogen therapy might have to be renewed. But, since the uterus has been removed, the best method of administration would be by means of a *single* subcutaneous implant of 50 or 100 mg. oestradiol. Such an implant is slowly absorbed in decreasing amounts during 3 to 6 months, and this ensures gradual reduction of dosage. When the effect has disappeared no further oestrogen therapy should be necessary. This treatment is unlikely to have any immediate or remote ill-effects.

Portable Cardiac Pacemakers

Q.—*In what type of case is a portable cardiac pacemaker likely to be useful?*

A.—A portable cardiac pacemaker attached to the patient may be indicated in persons with frequent syncopal attacks due to ventricular asystole (Stokes–Adams attacks) caused by complete heart block. Often such attacks can be prevented by the use of drugs, but some patients continue to have frequent and obstinate attacks of ventricular asystole, and in these circumstances some form of pacemaker is indicated. Patients who have long-standing or permanent complete heart block resulting from closure of a ventricular septal defect may also need a pacemaker, for they may be unable to maintain a satisfactory blood-pressure at a slow heart rate. Usually, however, the pacemaker can be discontinued after 3–4 weeks.

The principle of the pacemaker is to stimulate the ventricles to contract at a physiological rate so that the heart is "driven" electrically. Regular small electrical stimuli are delivered to the ventricle at a predetermined rate which can be varied as required. External stimulation may be used in an acute attack of ventricular standstill by placing electrodes on the chest and applying a shock which is transmitted to the myocardium. This method, while invaluable under such circumstances, is unsuitable for long-term use, because of local pain, discomfort from the contraction of chest wall muscles each time the shock is applied, and the risk of skin burns from the electrodes.[1]

Direct stimulation by means of electrodes implanted in the ventricular myocardium[2] is now a well-established practice. The myocardial electrode is connected by a wire passing through the chest wall to a small pacemaker powered by batteries. This method is painless, but often becomes ineffective after a few weeks owing to a rising threshold for stimulation due to tissue reaction around the electrode. Other risks are the sudden loss of electrical contact and the introduction of infection into the heart. Experiments in dogs have resulted in the development of myocardial electrodes of platinum insulated with "teflon," which have remained effective for as long as 8 months.[3] Electrodes have been introduced into the ventricle by blind percutaneous puncture, but this method is hazardous and not to be recommended. Thoracotomy is generally required for safe and effective implantation of the electrode, although this has been avoided by introducing the electrode into the right ventricle through a cardiac catheter passed from a peripheral vein; but thrombosis, embolism, and cardiac arrhythmia are considerable hazards of long-term use of this method.

The rate of stimulation varies with the needs of the individual and should usually be between 70 and 90 beats per minute in adults, but faster rates may be required in children: it is essential that an adequate systemic blood-pressure be maintained. The current required for direct ventricular stimulation being small, pocket-sized pacemakers present no great problem, and such an instrument could be attached to, or sewn into, the chest wall.

However, the risks attendant upon pacemaker wires passing through the skin of the chest wall are considerable when long-term use is indicated, and a transistorized battery-operated pulse generator and radio-frequency transmitter that transmits a signal through the skin has been developed.[1] A small transistorized diode detector is placed subcutaneously, receives the signal from the radio transmitter, and delivers the stimulus to the ventricle by wires which thus never pass through the chest wall. This method has been used clinically.[3,4] However, a disadvantage is the need for constant close proximity of the external transmitter to the subcutaneous receiver.[1] Finally, miniature pacemakers containing long-life batteries may be implanted beneath the skin of the chest wall. This method requires either surgical replacement of the unit and batteries at regular intervals before the latter fail, or implantation of rechargeable batteries which could be charged through the skin at intervals by an external radio-frequency transmitter.[1]

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Fat Babies and Delayed Walking

Q.—*I have the impression that babies who gain weight rapidly are slower to sit up and to walk than those whose weight gain is slow. Is this impression correct, and, if so, are there figures available to support (or refute) it?*

A.—I know of no figures to support or refute this suggestion, and certainly, in my personal experience, of nothing to support the observation. It is commonly said that a baby is late in walking because it is so fat, and it may be that this is in fact true of the excessively large fat baby. I would think it very doubtful that there is any significant difference in the time of sitting up and of walking between babies of above-average and less-than-average weight for age.

NOTES AND COMMENTS

Cleaning Syringes.—Dr. J. M. JEWITT (Eastwood, Notts.) writes: May I make two comments on the answer to your questioner's query about cleaning syringes ("Any Questions?" April 1, p. 980)? (1) Distilled water—"and consumption should be small." I find I have to replace 1–1¼ pints (0.6–0.85 litres) of water in my electric boiler-type sterilizer each day—surely not a small amount. (2) It is my experience that nylon syringes, such as the "vandermie," do not collect a deposit, whereas glass syringes do so in this district.

Dr. H. M. ELLIOTT (Sevenoaks, Kent) writes: Referring to the question on cleaning syringes, the deposit caused on glass from the use of hard water can be removed by soaking for a few minutes in ordinary vinegar. The deposit can then be wiped or brushed off without difficulty.

Dr. A. TODD (Durham) writes: I have found that a very satisfactory method of cleaning syringes which are "furred up" by hard water is to swab them with cotton-wool soaked in acetic acid, which quickly removes the incrustations.

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